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GENERALISED RHABDOMYOSARCOMA (RMS) PRESENTING LIKE LYMPHOMA OR LEUKEMIA - A DIFFERENTIAL-DIAGNOSTIC CHALLENGE

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Introduction: Generalised RMS is one of the rarest and most difficult differential diagnoses in paediatric oncology - especially for pathological evaluation. Within this report we describe 9 cases of the CWS studies 81 to 91 with this kind of generalised RMS.

Patients: **9 (7%)** of 131 pts. (≤21 yrs., CWS-81 to 91) with initial metastatic RMS (stage-IV) presented clinically with huge lymphoma masses or leukaemia-like blood cell counts, but **no primary tumour**. Since the suspected diagnosis in all cases was lymphoma or ALL, they underwent lymph node biopsies or bone marrow aspiration, some few even fine needle biopsies of bone lesions. 7/9 pts. presented with extensive bone marrow invasion (80%-91% tumour cells) and 7/9 with several skeleton metastases. Huge lymph node metastases were found in 3/9 pts., but the lungs were only affected in 2/9 cases, which is quite different to other stage-IV RMS. Other sites included multiple liver metastases (2/9) and soft tissue (1/9). Sometimes very difficult histopathological evaluation (including immunhistochemistry) finally led to the diagnosis of an alveolar (6/9, RMA) or embryonal (3/9, RME) RMS. The median age in this group was with 14 yrs. (range 2-19 yrs.) astonishingly high and sex ratio was equal with 5:4 (m:f).

Results: One pat. refused therapy due to the presumingly poor prognosis and died 6 weeks after diagnosis. All other pts. (8/9) received 2-5 cycles of chemotherapy (VAIA or CEVAIE), 1/9 received radiotherapy (40 Gy abdominal), and 3/9 resection of metastases - none received Mega-Dose chemotherapy (± rescue). Response to chemotherapy was heterogeneous with 1/9 complete, 2/9 good, and 1/9 partial responder. All other tumours (5/9) remained clinically stable or were progressive. First complete remission was achieved only in 3/9 (33%) cases. In summary, 8/9 cases (89%) died 5 to 16 months after diagnosis. Only one female patient (RME, 6 yrs., 1xVAIA+4xCEVAIE [13 months. total therapy duration!], no local therapy) is still in 1. continuos clinical remission (Follow/up: >6 yrs.) only affected by a intermediate-grade secondary Fanconi-Syndrome.

Conclusion: Generalised RMS presenting like lymphoma or leukaemia is fortunately a quite rare seen phenomenon in children and adolescents but regularly causing severe problems in diagnosis and therapy. Despite of new techniques in molecular diagnosis, sufficient biopsies are warranted for better histopathological evaluation. Prognosis in general is very poor, but especially in RME therapy intensification (by mega-therapy or elongation of therapy) and early local therapy (to achieve a higher rate of remissions) may be useful in providing better systemic and local control.

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CONCOMITANT CHEMO-RADIOTHERAPY FOR INCOMPLETELY RESECTED LOW-GRADE ASTROCYTOMA IN CHILDREN

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Background: Despite a favourable effect of postoperative irradiation in non-radically resected grade I and II astrocytomas, the long term survival rates in this patient group are relatively poor: at 5- and 10-year 35-76% and 14-28%, respectively. The aim of our study was to evaluate the effectiveness of concomitant chemo-radiotherapy after incompletely resected low-grade astrocytomas in 9 children, treated at our Institute in the period 1986-1992.

Patients and methods: There were 7 boys and 2 girls, aged 4-15 years, median 11 years. All tumors were supra-tentorial: cerebral hemispheres were involved in 5 patients and basal ganglia in 4 patients. Partial resection of the tumor was performed in 6 patients, only biopsy in 3; the extent of surgery was evaluated with CT and/or MRI studies. Postoperative radiotherapy using megavoltage equipment (6 or 8 MV X-rays beam) or a Co-60 unit, was given through two opposing lateral fields to the tumor bed, with a tumor dose of 50-56 Gy (median, 50 Gy), delivered in 1.8-2 Gy daily fractions. The time interval between surgery and the beginning of irradiation was 14-81 days (median, 42 days). Chemotherapy was intercalated in the radiotherapy protocol: cisplatin 12 mg/m^2/2 weeks and vincristine 1.4 mg/m^2/week, starting on day 1 of irradiation.

Results: Of 9 patients, 7 are alive, with no evidence of disease 4-9 years (median, 8 years) after treatment. One patient is alive, with tumor residue visible on CT after 10.5 years. Only one death was registered among our patients, 5 years after chemo-radiotherapy, due to a secondary grade IV astrocytoma, without recurrence at the site of the first tumor at the CT. All but one living patients are able to take care for themselves and live a normal everyday life; in patient with persistent disease only a mental retardation was recorded.

Conclusion: In view of our encouraging results a randomised study of the above-described postoperative chemo-radiotherapy versus radiotherapy, is presently going on.

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NEUROBLASTOMA (NB) IN ADOLESCENTS. CHARACTERISTICS, CLINICAL COURSE AND OUTCOME.

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NB commonly affects children in the first years of life with a peak incidence around 2 years (y). Since its occurrence in adolescents (age 10-18 y) is rare little is known about clinical and biological characteristics of patients (pts) of this age. Between 1979-1995, 30 adolescents with NB were diagnosed in 23 Italian institutions. Sixteen were male and 14 female; median age was 147 mos (range 120-216). Primary tumour was located in abdomen (22), thorax (6), pelvis and thoraco-abdominal region (one case each). According to INSS 13 pts had localised (stage 1-3) and 17 metastatic disease (stage 4). Histology (according Shimada) was reviewed in 24 pts and found favourable in 8 and unfavourable in 16; 3/17 pts had MYCN gene amplification and 8/18 had diploid or tetraploid DNA content. In stage 4 disease uncommon metastatic sites were detected: lung (3), liver (2), brain (1), kidney (1), pleura (1). Pts were treated according to stage with same modalities of children aged 1-9 y diagnosed in the same period. Compared with these latter pts adolescents had a 5-y overall survival (OS) of 33% *v* 40% (p=.07) and an event-free survival (EFS) of 15% *v* 35% (*P*=.08). In particular adolescents with localised disease had a worse prognosis (OS 37% *v* 69%; *P*=.18; EFS 18% *v* 64%; *P*=.011) while in stage 4 the course of disease was similar in the two age ranges (OS 30% *v* 20%; *P*=.28; EFS 0% *v* 15% *P*=.4). In conclusion adolescents with NB tend to have a poor outcome independently on stage. Their clinical and biological characteristics and response to therapy deserve further clarification.

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ALPHA-FOETOPROTEINE (AFP) SECRETING MALIGNANT EXTRACRANIAL GERM CELL TUMORS (GCT) IN CHILDREN : EXPERIENCE OF INSTITUT CURIE BETWEEN 1977 AND 1995

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Aim of the study : To retrospectively review the cases of AFP secreting GCT treated at Institut Curie between 1977 and 1995. **Patients and methods** : They were 47 pts (27 boys, 20 girls) with a median age of 2 years (y) (range : 2 months (m)-16 y). Median duration between symptoms onset and diagnosis was 1 m (range : 0-10 m). Associated particularities were chromosomal abnormalities (2) gemellarity (1), precocious puberty (1), congenital malformation (1), previous mature teratoma (1). The primary site was testis (20), ovary (11), sacrococcyx (9), retroperitoneum (4), mediastinum (3). Histological types were yolk sac (23), mixed tumor (24). TNM stages were : I (15), II (9), III (15), IV (8). Following the French Society Pediatric Oncology criteria, a high risk (HR) or a standard risk (SR) was considered to be associated to AFP levels ≥ or < 15000 ng/ml. From 1977 to 1984 chemotherapy protocol was MAC regimen (MTX,

ACT D and CPM) and CDDP, Velbé (V), Bleomycine (B), Adriamicin (ADR) (17 pts). Between 85 and 89, TGM 85 protocol used alternating courses of : V, B, CDDP/ A-CPM (15 pts). Between 90-94 TGM 90 used the same combination with Carboplatine instead of CDDP (15 pts). **Results :** In 45 evaluable pts there were 21 HR children med=50000 (range 15.500-321.000), and 24 SR med=500 ng/ml (range 20-13.400). AFP >50.000 was observed only in the stages III (4/15) and IV (5/8). Initial treatment was surgery in 30 pts : complete (15), incomplete (15). Tumoral rupture was observed in 6/47 pts (13%) : spontaneous (3), per-operative (3). The chemotherapy was neoadjuvant in 17pts and adjuvant in 23. High dose CT with ABMT was used in 3 pts (2PR and 1 PD). Tumor response was evaluable in 46 pts evaluable : CR in 39 pts (84,7%), PR in 2 and PD in 5. 9 pts relapsed locally (23%) amongst them 4/9 had sacrococcygeal tumors, one a bilateralization in the ovary. The median interval between the end of treatment and relapse was 4 m (range : 1-12 m). Treatment of relapses included HD CT in 5, and RT in 6 children (2 thorax , 4 pelvis). 40/47 pts are long term survivors (33 in CR1 with 10 y median follow-up fu) 7 in CR2 with 7 y median fu. 7 pts died : 4 of disease progression, 2 early post-operative and one of CT toxicity. Therapeutic sequelae were : unilateral castration (24), bilateral castration (1), ototoxicity grade IV (3), decreased pulmonary function (4). Second benign tumors ocurred in 2 cases : mature teratoma and lipoma. **Conclusion** : **1** - Overall survival rate of this group of patients is 85% and 18% of them are in CR2. **2** - There seems to be a correlation between clinical stage and AFP level. **3** - Survival of HR pts (86%) is not different of SR PTS (92%). **4** - In spite of initial tumoral rupture, 4/6 pts are long term survivors.

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COMBINED ADJUVÁNT CHEMOTHERAPY IN MALIGNANT PEDIATRIC BRAIN TUMORS - PRELIMINARY RESULTS

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Malignant brain tumors of childhood represent a growing challenge for pediatric oncologists, radiotherapists and neurosurgeons. Overall survival rates of posterior scala tumors in children were cca. 30-40% at the beginning of the 90's in Hungary. Based on previous favorable results in relapsed medulloblastoma patients treated with a dibromodulcitol based chemotherapy a new protocol was initiated in 1991 to improve survival in this patient group. 47 patients have entered the protocol since 1991, 29 of which were medulloblastomas, 8 ependymomas, 5 astrocytomas, 2 choroid plexus tumors, 1 primary neuroblastoma, 1 teratoma and 1 PNET. 20 of the patients were considered high risk because of residual mass, tumor cells in cerebro-spinal fluid or brain stem involvement (47%). Patients received chemotherapy in a sandwich design, prior to and following craniospinal and local-boost irradiation. Chemotherapy regimen consisted of cycles with vincristine-dibromodulcitol-procarbazine, methotrexate-etoposide, cisplatin-etoposide plus inthratecal therapy. 5 of 47 patients are still on therapy. 44 (91%) patients have achieved CR, 4 have achieved PR, 3 of these later progressed, 8 patients relapsed (17%). 9 patients have died (19%), 6 because of relapse and progression, 2 of progression, 1 of infection. Overall survival is 83% at 5 yrs, tumor-free survival is 74 %. Bone marrow suppression was the leading toxicity, with extreme prolonged suppression periods in some cases after finishing therapy (more than 20 weeks). Median observation time is 23 months (2-63). Follow-up time is still short but these preliminary data suggest improval in response rates and survival times and warrant further studies for refining the protocol and decreasing toxicity.

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ADULT TYPE MALIGNANT TUMORS IN CHILDHOOD

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Carcinomas and other related tumors are rare in childhood. Thirty-two children with these types of tumors representing <3% of total, were referred, treated and followed at the Oncology dept of childrens' Hospital A.Kyriakou from 1980 to1994. Thyroid cancer and non-rhabdo soft tissue sarcomas were excluded from this material. Of these 32, 8 had nasopharyngeall (NP), 5 hepatocellular (HCC), 2 renal cell carcinoma, 5 non germ-ovarian tumors, 4 cortical adrenal tumors and 8 miscellaneous (thymoma, basal cell skin, squamous cell tongue, bronchogenic, pancreatic carcinomas, CNS melanoma, carcinoid tumors). More than half (17/32) were adolescent at the time of diagnosis, 19/32 were female and 13/32 (all NP, 4/5 HCC, 1/2 renal) had metastatic disease. Metastases were documented in lymph nodes (NP), in lungs ± bones (HCC) and in liver (renal). Complete surgical removal of the tumor was achieved in adrenal and ovarian. tumors. Chemotherapy as per medical Oncology guidelines was administreted in 21/32 patients (all NP, all HCC and in others) and radiotherapy in 11/32. In 2 patients with adrenal cortical carcinoma O-P-DDD was given. Twenty patients are alived and disease - free for a median time of 12 years (2 - 17).
Conclusion: Adult type malignant tumors in childhood are rare with clinical characteristics, therapeutic internvention and prognosis not different to similar diseases in the adult life.

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DYNAMIC MR IMAGING OF OSTEOSARCOMA RESPONSE TO CHEMOTHERAPY

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Objective: To evaluate the effectiveness of dynamic contrast-enhanced magnetic resonance imaging (DEMRI) for determining osteosarcoma response to preoperative chemotherapy.

Methods: We performed DEMRI studies on 39 patients with osteosarcoma, treated with three cycles with ifosfamide/carboplatin followed by resection. During the routine MR imaging procedure, 30 sequential flash images of a representative section of tumor were collected over a seven minute period during, before and after IV bolus injection of 0.1 mmol per kg gadolinium-DTPA, a paramagnetic contrast agent. The histopathologic grade of response was determined from a similarly oriented section of the resected tumor and compared with the average dynamic vector magnitude (DVM), a parametric measurement of enhancement calculated from the initial contrast accumulation rate and maximum tumor enhancement.

Results: Tumors with higher average DVM values at presentation had greater decreases in the parameter over the course of therapy and the average DVM value immediately prior to surgery accurately indicated histopathologic grade of necrosis in 35 of 39 patients.

Conclusion: DEMRI analysis before surgical resection accurately measures tumor necrosis in osteosarcoma. DVM reflects tumor perfusion and may be a useful surrogate for evaluating delivery of chemotherapy.

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THE IMPORTANCE OF SPLEEN SONOGRAPHY FOR THE STAGING EXAMINATION OF HODGKIN'S DISEASE IN CHILDHOOD AND ADOLESCENCE

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The importance of the imaging modalities for the assessment of a potential infradiaphragmatic involvement in the staging examination in Hodgkin's disease in childhood and adolescence has clearly increased in the last 10 years. For a long time laparotomy was considered to be an obligatory precondition for staging. Since 1985 selective laparotomy in German-Austrian pediatric HD-studies was restricted to children for whom the imaging procedures were suspicious of abdominal involvement.

Patients and Methods: In the present study we have limited even more the indication for laparotomy: laparotomy is only carried out in cases in which an abdominal involvement cannot be defined by imaging modalities. Experience from previous studies and the evaluation of the current GPOH-HD 95 study which includes 210 patients to date prove the higher sensitivity of sonography concerning the assessment of spleen involvement in comparison with CT/MRI. Sonographic criteria for spleen involvement are most importantly: 1.) local lesions either solitary or multiple, either round or oval or irregularly limited, either hypo- or vary rarely hyperechoic or 2.) diffuse disorganization of the parenchyma with or without spleen enlargement.

Results: An infradiaphragmatic involvement was diagnosed in 59 out of a total of 210 patients of the study (28.9%) and 41 of these (19.5%) had spleen involvement. For these 41 patients spleen involvement could be diagnosed in 29 patients (70.7%) by CT/MRI as well as sonography, in 12 patients (29.2%) only by sonography (CT/MRI negative!) and in 3 patients (7.3%) only by CT (sonography negative!). The earlier HD studies had shown similar results for large numbers of patients, frequently proved by additional laparotomy.

Conclusions: Our results suggest that the sonography of the spleen has a higher sensitivity than CT/MRI for the detection of a spleen involvement in Hodgkin`s disease. It is still necessary to combine sonography and CT or MRI for the staging procedures in Hodgkin's disease.
We present some typical sonographic findings of spleen involvement for which the CT/MRI diagnoses were negative.

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PLACE OF THE GALLIUM-67 SCINTIGRAPHY IN THE FOLLOW-UP OF PATIENTS WITH MEDIASTINAL HODGKIN'S DISEASE (HD).

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In HD, the persistence of a residual mediastinal mass after treatment raises questions on tumor vitality.
The aim of this study is to determine the value of Gallium-67 (Ga 67) scintigraphy for follow-up in patients (pts) with mediastinal HD.
Patients and methods : Between September 1990 and December 1996, 21 pts,14 boys and 7 girls, of 5 to 15 years (y) of age (median 12 years 6months), with mediastinal localisation of HD were analysed. The histological type of HD was 1 (1 pt), 2 (15 pts) and 3 (5pts). Ann Arbor stage was II (8 pts), III (4 pts) and IV (9 pts) ; visceral disease for stage IV pts was the lung in 6 pts, the bone in 3 pts, the bone marrow in 3 pts and the liver in 1 pt.11 pts /20 have B and /or b symptoms. Initial imaging for all pts included : ultrasonography, computed tomography scan (CT) and Ga-67 scintigraphy. All pts are treated with the French Society of Pediatric Oncology protocol for stage II and III and SIOP protocol for stage IV.
Results : At diagnosis, 18/21 pts have positive Ga-67 scan in the mediastinum area. After chemotherapy, tumour response assessed by CT was : CR (5pts), PR >70% (13 pts) and PR <70% (3pts). 6 pts have positive Ga-67 scan : 4/13 pts with partial response (PR) >70%, and 2/3 pts with PR<70% at CT. At the end of the treatment tumour response was : CR (10pts), PR>70% (10pts) and one non evaluable patient who is undergoing radiotherapy. Only 1 pt had positive Ga-67 scan. This pt (stage IV (bone) Ab) who is in PR> 70% , had received a boost of 15 Gy in this tumoral site which was not histologically assessed. Surgical biopsies have been performed for three pts (2 stage II, 1 stage IV) because of minimal residual nodes at CT (but negative Ga-67 scan) with fibrosis at histological examination. 1 of these 3 pts relapsed 18 months after the end of treatment.
Conclusion : In this study, Ga-67 scintigraphy did not contribute to the assessment of the residual mass at the end of treatment ; but further investigations are needed.

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ROLE OF GA-67 SCANS IN CHILDREN WITH MEDIASTINAL HODGKIN'S DISEASE (HD).EXPERIENCE OF A SINGLE INSTITUTION

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Ga-67 scan is a sensitive method of detecting mediastinal involvement in HD. We report herein a retrospective study based on 24 children with mediastinal involvement, treated at the Gustave-Roussy Institute.
Methods: Thirty-eight Ga-67 scans were performed, at diagnosis (24), during and after therapy (14), on 24 patients (pts) (14 boys, 10 girls, median age:11 years) with mediastinal HD defined by a positive CT scan of the thorax. The incidence of stages I, II, III, IV was 1, 9, 5 and 8 respectively. Fifteen pts had B symptoms. Tumour types revealed mixed cellularity (15 pts), nodular sclerosis (7 pts). Children were treated according to current protocols of the French Society of Pediatric Oncology; 22 of 24 pts are alive (follow-up:30 months); 6 pts recurred. Dosages of Gallium isotope were not standardized.
Results: At the time of diagnosis, 17 pts have a positive mediastinal Ga-67 scan (false negatives:30%). Age, sex, tumour stage, B symptoms, were not significantly different in the group without mediastinal Ga-uptake. Six of 11 children tested during their preradiotherapy treatment achieved normal Ga-67 scan, despite persistence of radiologic abnormalities in 4.
Nine patients had residual abnormalities on CT scan : 2/3 with positive Ga-scans recurred versus 0/6 with negative Ga-scans. None of the 7 pts (including 3 pts with stage IVB) with initial negative scans recurred.
Conclusion: More than in adults, mediastinal Ga-67 scan is a delicate test in children with HD. Physiological mediastinal uptake of Ga-67 makes evaluation of disease difficult, at diagnosis or after treatment. Prognostic value of an initially negative scan needs more extensive prospective trials.

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SOCIOECONOMIC FACTORS IN THE FAMILIES OF CHILDREN WITH LEUKAEMIA AND LYMPHOMA. CONSANGUINITY IS ASSOCIATED WITH THE DIAGNOSIS OF LYMPHOMA.

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There are wide variations in the relative incidence of lymphoid malignancies in different parts of the world. We have previously shown a higher relative frequency of acute lymhoid leukaemia (ALL) among

children of subcontinental origin living in the UAE. Conversely, children of Arabic origin had a higher relative frequency of Hodgkin's disease (HD) and Non-Hodgkin lymphoma (NHL).
Patients and Methods: To analyze the role of social and genetic factors in the above difference, a socio-economic study was conducted through personal interviews among the families of 115 children with a lymphoid malignancy.
Results: In a univariate analysis of ethnic associations, smaller family size, and a higher parental education level was found in the subcontinental families. Income was higher in the families of children with HD and ALL as compared with NHL. Consanguinity was more frequent in the Arab, than in the Subcontinental families.
In a multivariate analysis, using diagnosis as the dependent variable, consanguinity was strongly correlated with the diagnosis of lymphoma.
Conclusions: These results suggest that socioeconomic factors play a role in the observed higher relative incidence of ALL in subcontinental families, lending support to the infectious aetiology of leukaemia. The association of consanguinity with lymphoma, also reported among Arabs in other countries and among Pakistani families in the UK, could reflect genetic differences but is more likely to stem from socioeconomic differences associated with ethnicity.

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PATTERNS OF CHILDHOOD CANCER IN EGYPT

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Pediatric Oncology Unit of Abu El Reech New Children Hospital (POCH) is a specialized clinic attached to Kasr El Eini Center of Oncology, Cairo, Egypt (NEMROCK). The current study is a descriptive hospital based registry and included 1007 children starting with the first patient referred to POCH on January 1st, 1991 and ending with the last patients accessioned into POCH registry by the end of 1995. Out of the 1007 cases accessioned into the registry, 988 children were confirmed to have a histological proof or a laboratory evidence of cancer. The relative frequency of childhood cancer was 9.57% (988/10320) of all cases with malignant neoplasms referred to NEMROCK and POCH registry during the period between 1991 and 1995. Among our patients, leukemias and lymphomas represented 44.8% of all pediatric cancers followed by neoplasms of the central nervous system (20%), neuroblastoma (8.7%), Wilm's tumor (6.4%), soft tissue sarcoma, retinoblastoma, germ cell tumors. The relative frequency of leukemias and soft tissue sarcomas are more or less stationary in the different age groups. However, the relative frequency of lymphomas and bone tumors increases with age and that of retinoblastoma, neuroblastoma and Wilm's tumor decreases with age. On the other hand, the relative frequency of brain tumors and primary hepatic tumors increased with age. This observation is in contrast the report of the National Cancer Institute, where the primary neoplasms of the central nervous system and liver decrease with age. This may be attributed to host and environmental factors. The effect of the environment is most evident for neoplasms of the liver as 30% of our patients with primary hepatic neoplasms were diagnosed to have hepatocellular carcinoma on top of liver cirrhosis. The occurrence of liver fibrosis during childhood among our patients may be related to dietary or environmental factors (Hepatitis C virus, bilhariziasis) and should be studied further in detail.

The majority of pediatric malignant diseases have vague or benign symptoms that usually resemble those of the more frequently encountered benign diseases as arthritis, coagulation disorders and infection. Therefore, the majority of our patients present with advanced disease.

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Risk Factors for Childhood Leukemia.

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A population-based, prospective, multi-centre case-control study of factors relating to the risk of all childhood leukemias has been carried out in five provinces in Canada. A total of 451 eligible cases were identified; data for 399 case-control pairs were available for analysis. Information was collected on socioeconomic and demographic variables, genetic and familial associations, and factors affecting immune response to infections, as well as the mother's reproductive and pregnancy experience, and parental and childhood exposures to ionizing radiation and chemicals (including drugs and medications). Significant odds ratios (OR) with 95% confidence intervals (CI) are presented for preliminary results adjusted for age, gender, and province. A significant protective effect with increasing age of either parent was observed (OR for mother = 0.59, CI=0.4,0.8; OR for father =0.58, CI=0.4,0.9). Parents' education beyond high school was protective (OR=0.56, CI=0.4,0.9 for mothers, OR=0.65,CI=0.5,0.9 for fathers), as was increased household income (OR=0.60,CI=0.4,1.0). Other protective factors included measles, mumps, rubella vaccination of the child (OR=0.41, CI=0.2,0.9); child's reported chicken pox (OR=0.68, CI=0.5,0.9); or reported use of immunosuppresants or steroids (OR= 0.42,CI=0.2,0.9). Excess risk of leukemia was seen with non-Caucasian heritage (OR=1.46, CI=1.0,2.1), mothers' use of oral contraceptives at the time of conception of the index child (OR=1.70, CI=1.0, 3.0), or any smoking of the mother during pregnancy (OR=1.44, CI= 1.1,1.9). In the year before the index child's birth, fathers' smoking (OR=1.31, CI=1.0,1.7), use of megavitamins (OR=1.89, CI=1.0,3.6), or use of behaviour-altering drugs (OR=1.64, CI=1.0,2.6) showed excess risk.

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FAMILIAL OSTEOSARCOMA

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Of 341 patients admitted to our hospital with osteosarcoma between March 1962 and November 1996, 13 cases occurred in 6 families, with more than one family member affected with osteosarcoma. The family relationships included a male patient and his maternal grandfather and maternal great uncle, two male patients and their nieces, two cousins, brother and sister, and mother and son, each with osteosarcoma. Median interval between diagnosis of affected individuals as determined for five kindreds was 9.7 years (range 5.8 - 24.9 years), but was unknown for the patient whose maternal grandfather and great uncle had their diagnosis prior to our patient's diagnosis. Two families have pedigrees consistent with the Li-Fraumeni syndrome. Testing for abnormalities of the p53 gene has been performed for at least one member of three families, of which only one demonstrated abnormalities; this positive test was demonstrated for a patient with osteosarcoma and colon carcinoma. Eight of our 13 affected patients have died, six of osteosarcoma, one from recurrent osteosarcoma and colon carcinoma, and one from gastric carcinoma. The primary sites, treatments, metastatic patterns and survival time of the patients who died of osteosarcoma did not differ significantly from that of our entire patient population who died of osteosarcoma. The relationships among

the family members with osteosarcoma and the interval between the occurrence of osteosarcoma in these six families demonstrates the need for continuing epidemiologic surveillance long after the diagnosis of osteosarcoma within any family (Supported by USPHS Grants CA23099 and CA21765, and by ALSAC).

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Pediatric Non-Hodgkins Lymphoma Involving Bone: A Review of the Hospital for Sick Children Experience (87-96)

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OBJECTIVE: To evaluate symptoms at presentation, prognostic factors and outcome of NHL with bone involvement.
Methods: Retrospective chart review at single institution , HSC (1987-1996)
Results: Of 195 cases of NHL, 16 (8%) patients with bone involvement were identified: 4 females and 12 males. The mean age at diagnosis was 10.4 yrs (4-16.5y). 14 had symptoms relating to bone at presentation (pain, mass, limp). Site of involvement included long bones (10), pelvic(4) , vertebral (4) , skull (3). Lesions were lytic in 12 , lytic and sclerotic in 4. Extraskeletal involvement occurred in 11 patients: bone marrow in 1, soft tissue mass in 4, liver in 1, kidney in 1, regional and distant nodes in 2, paraspinal in 3. Staging was as follows: stage I:1, stage II: 3, stage III: 10, stage IV: 2. 9 were large cell lymphomas, 7 were small non-cleaved cell. 4 were Ki-1 positive, 1 had a t(2,5). All patients were treated with multiagent chemotherapy regimens (Berlin Protocols 12, POG 9315 2, POG 9317 1, LSA-L2 in 1). 1 patient also received radiation to affected bone. 4 patients relapsed. 1 on treatment, 3 between 19-23 months post therapy. 2 of the relapsed patients died of progressive disease. 12 (86%) of the patients are now disease free at 16-109 months. 2 are still on treatment.
Conclusion: Unifocal or multifocal bone lesions, and location of primary site were not of prognostic significance. Finding of extraskeletal involvement in bone marrow, kidney, and skin at diagnosis were significant. 86% survival has been achieved with multimodal chemotherapy regimens for pediatric NHL involving bone.

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OVARIAN LOCALISATION OF BURKITT'S LYMPHOMA : A CLINICAL STUDY OF 17 CASES.

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Purpose : Between 1981 to 1995, 48 girls were referred for Burkitt's lymphoma to pediatric departement of the Institut Gustave Roussy. 17 of them (35%) had an ovarian involvement and are the subject of this study. **Results** : The average age was 8.4 years. Main symptoms were isolated ovary mass in 6 cases (35%) (bilateral : 3, unilateral : 3), pelvic mass in 5 cases (29%). Surgery had allowed to discover ovarian involvement in 5 cases (29%) : in 4 cases, salpingo-oophorectomy was performed before admission (unilateral : 3 ; bilateral : 1) and in one case later on emergency surgery. In the other cases, (71%) abdominal ultrasonography performed at admission allowed to suspect ovarian involvement when ovary was enlarged and had a solid homogenous aspect. According to St Jude's staging system, 14 patients (82%) were stage III and 3 (18%) were stage IV (2 CNS +, 1 BM +). Primary site was abdominal in 16 cases (94%) and jaw in 1 (6%). Among the other abdomino-pelvic organs, kidney were involved in 3 cases, liver in 2 cases and pancreas in 1 case. In 8 cases, retroperitoneal nodes were enlarged. 2 girls were treated according to LMB 81, 5 to LMB 84, 2 to LMB 86 and 8 to LMB 89. Unilateral ovarian residual mass was found in 6 cases (35%) and histopathological study (4 biopsy, 2 unilateral radical surgery) showed no Burkitt's lymphoma. CR rate was 100%, one girl died after abdominal relapse and 16/17 girls are alive in RC1 (94%) (median follow-up : 9 years). At diagnosis, 4 girls (23.5%) were pubescent and have no problem actually, 13 (76.5%) were no pubescent. Among them, puberty age is not reached for 2 girls, one is died of disease, 7 are normally pubescent and for 3 girls data concerning puberty status is not available. Among no pubescent girls at diagnosis, 4 had bilateral involvement without bilateral surgery. 3 of them are normally pubescent and for 1 no data is avalaible . **Conclusion** : Ovarian involvement is frequent in Burkitt's lymphoma (35%) Abdominal ultrasonography allows to suspect a majority of them. Radical surgery seems to be uselessness to establish diagnosis and for residual mass probing. We express the possibility for girls to have normal endocrine ovarian fonction.

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T-CELL LYMPHOMA AND T-CELL LEUKEMIA AT SCHNEIDER CHILDREN'S MEDICAL CENTER OF ISRAEL (SCMCI). LAST 12 YEARS EXPERIENCE.

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Between 1984 and 1996, 20 children with T-lymphoma (Ly) and 54 with T-ALL were newly diagnosed at SCMCI. Differences in incidence of patient's origin were noticed: in T-Ly, only 5% of patients were of Israeli Arab origin while in T-ALL, they were 25% of patients. It is of note that T-ALL is more frequent among Israeli Arabs compared to Israeli Jews (40% vs. 24% of ALL, respectively). Age distribution and male predominance were similar in both groups. Clinically, larger mediastinal masses were more frequently encountered among T-Ly usually accompanied by pleural effusion. By immunophenotype in both groups, CD7, CD5, CD2 were strongly positive in most patients (~90%), CD4 and/or CD8 in the majority of them (~70%), CD3 in lower percentage (~50%), and CD1 in only 30% of T-ALL and, 50% in T-Ly.
T-Ly was treated as T-ALL. Between 1984 and 1989, treatment with multiagent repeated courses was applied and since 1989, the ALL-BFM-86 based protocol was introduced. Relapses on the first protocol occurred in: 3/12 patients with T-Ly and 12/20 patients with T-ALL and on the BFM-based protocol, with a shorter follow-up: in none of the 8 patients with T-Ly, and in 8/27 with T-ALL. Failures occurred mostly in poor steroid responders.
Although many common features exist between T-Ly and T-ALL, the differences in incidence of ethnic origin may suggest different underlying pathogenetic mechanisms of these T-lymphoproliferative malignancies.

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LONG-TERM FOLLOW-UP OF LATE EFFECTS OF TREATMENT IN 45 SURVIVORS OF CHILDHOOD LYMPHOMAS

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Patients and methods: Forty-five long term survivors of histology-proven childhood lymphomas were evaluated according to clinical staging at initial diagnosis [11/71-12/89] for pulmonary function, sonographic abnormalities of the thyroid gland, semen analysis, cardiac electrocardiography, echo Doppler cardiography and endocrine profile. The 26 male patients [pts] and 19 female pts, ratio 1.34:1, were diagnosed with Hodgkin Disease [HD] - 26 pts, Burkitt Lymphoma - 12 pts, Non Hodgkin Non Burkitt Lymphoma [NHNBL] - 7 pts. Mean age at diagnosis: 9.1 years [y] [range, 2.1-16.4 y], mean age at follow-up: 21.1 y [range, 8.9-33.7 y], mean follow-up duration: 10.9 y [range, 3.9-22.2 y], Treatment: HD - CT: MOPP - 10/26, MOPP/ABVD - 14/26; RT - Mantle:26/26, Inv. Y - 5/26, Paraaortic - 2, Spleen - 3, Total nodal - 1. BL - CT: COMP - 8/12, NCI - 3/12, LMB - 1/12. NHNBL -CT: LSA2L2 - 4/7, COMP - 2/7, LSA2L2/COMP - 1/7; RT: Brain - 2/7, Mediastinum - 2/7.
Results: Abnormal pulmonary function: HD - 9/26 pts, restrictive - 3, obstructive - 3, decreased diffusion capacity - 4. 2/9 pts had clinical symptoms. BL - 2/12 pts, obstructive - 1, decreased diffusion capacity - 1. NHNBL - 0 pts. Ultrasonographic abnormalities: HD - 14/26 pts, solitary nodules - 4/14, all received mantle irradiation; hypothyroidism: 14/26 pts, 8/14 had sonographic abnormalities. 1 thyroid papillary carcinoma. Semen analysis: normal values - 4/20 pts, oligospermia - 8/20 pts, azoospermia - 8/20 pts. FSH above normal - 10/20 pts, 4/5 who received Inv. Y irradiation were azoospermic, 1 was severely oligospermic. Cardiac involvement: prolonged QTc interval: HD - 4/26, BL - 3/12, NHNBL - 1/7. Incomplete RBBB: 4 pts; complete RBBB: 2 pts; MVP: 1pt. Flow: MR - 7/45 pts. Second primary cancers: 1 pt developed neck fibrosarcoma, 1 pt developed thyroid papillary carcinoma.
Conclusions: Abnormal pulmonary functions are common but rarely associated with clinical symptoms. Mantle irradiation is associated with a high incidence of thyroid pathology. Treatment damage to the testis involves tubular germinal elements. RT and CT with nitrogen mustard and cyclophosphamide were associated with high rates of oligospermia and azoospermia. MOPP/ABVD combination did not have a significant better outcome of sperm counts compared to MOPP alone. Age at CT did not correlate with the sperm count. Prolonged QTc interval was not associated with SA or AV node dysfunction-conduction anomalies. Mitral flow abnormalities were above expected prevalence. Evidence of significant long-term complications resulting from polyCT and RT emphasizes the need for further research for newer therapies which maintain effectiveness on the underlying disease while producing fewer toxic effects.

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Osteopenia in Children Surviving Brain Tumours

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Objective: Osteopenia has been reported in children surviving acute lymphoblastic leukemia, apparently as a consequence of therapy. It has been suggested that cranial irradiation may play a crucial role in this disorder. To explore that possibility, survivors of brain tumours in childhood, all of whom had received radiotherapy, were examined for evidence of bone mineral loss.

Methods: Nineteen children were assessed, on average at 7 years after treatment. Measurements of growth velocities, plain radiography of the skeleton, bone densitometry, health–related quality of life and physical activity were undertaken.

Results: Growth hormone (GH) deficiency had been detected in 6 children and 5 had received GH replacement for a minimum of more than 3 years. Nine children were radiographically osteopenic, including the 5 who had received GH. Z scores for bone mineral density (BMD) were negative in the majority of children. Health–related quality of life was less and pain more frequent in those with low BMD scores. Pain was correlated negatively with both free time activity and seasonal activity ($p<0.01$).

Conclusions: Osteopenia is a common sequel of therapy in children with brain tumours. Those with osteopenia have more pain and more compromised, health–related quality of life than those who are not osteopenic, and pain significantly limits physical activity. The pathogenesis of osteopenia in these children remains uncertain but is likely multi factorial.

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Health–Related Quality of Life in Survivors of Wilms' Tumor and Advanced Neuroblastoma – A Comparative Study

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Objective: Children with Wilms' tumor undergo relatively "mild" chemotherapy and have an excellent prospect for cure in contrast to those with advanced neuroblastoma who are treated very intensively yet face a low probability of long–term survival. We hypothesised that survivors of these two disorders and treatment programmes would manifest respectively low and high burdens of chronic morbidity as assessed by measures of health–related quality of life (HRQL).

Methods: The families of children who had completed therapy for Wilms' tumor (stages 2–5) or advanced neuroblastoma (stage 4 and inoperable stage 3) at two Canadian institutions, and who were on active follow–up, were invited to participate in the study. Those who agreed were sent by mail 15 item questionnaires on the health status of their children, to be completed independently by a parent and the child (if he/she was ≥8 years of age). The responses were mapped by an algorithm into vectors of the Health Utilities Index Mark 2 and Mark 3, from which scores for HRQL were derived using a multi–attribute utility function based on community preferences.

Results: Responses by parents of children who had been treated for neuroblastoma (n=32) provided importantly lower mean utility scores (0.885±0.139, p=0.03) than those by parents of children who had had Wilms' tumor (0.946±0.072, n=61). By contrast, the mean utility scores from responses by children in the two groups were not significantly different (Wilms' tumor: 0.941±0.059, n=33; neuroblastoma: 0.939±0.099, n=13). Furthermore, mean utility scocres provided by the parents of the children who were able to respond themselves were very similar (Wilms' tumor: 0.944±0.067; neuroblastoma: 0.933±0.109).

Conclusions: The greater burden of morbidity in survivors of advanced neuroblastoma, in comparison to survivors of Wilms' tumor, as perceived by proxy respondents (parents), may reflect compromised HRQL particularly in children who cannot assess their own health status.

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STAGE 4 NEUROBLASTOMA - THE COST OF CURE

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Stage 4 Neuroblastoma (Nbl) is difficult to cure but 15-20% of our >1 year old patients (pts) are disease-free >5 years after treatment.

The **Objective/Methods** of our study were to determine late sequelae in 14/19 stage 4 available survivors and 2 stage 3 pts similarly treated here between 1979-1988. Fifteen pts received cisplatin-based 'induction' chemotherapy (OPEC) alone (9) or with Ifosphamide (3) and/or doxorubicin (6). All 16 then received high dose melphalan (HDM) consolidation; 2 also received total body irradiation (TBI) and I ^{131}I mIBG. Mean age at diagnosis was 2.4 years, mean follow-up 10.6 years with mean age 13.2 years.

Results
Severe ototoxicity (Brock grade 3/4) occurred in 4 pts. Glomerular filtration rate (GFR) was 78 mls/min/1.73m^2 but lower (30-66) in 3 Ifosphamide- and radiation-treated patients. No heart failure occurred but shortening fraction was < 28% in 2/5 pts (mean doxorubicin dose 158 mg/m^2). Growth hormone replacement was required in both TBI-treated pts. No thyroid dysfunction was noted, but the mIBG-treated pt developed multiple benign thyroid nodules. Of 8 girls, 7 achieved menarche but 2 (both treated with TBI/mIBG) have severe ovarian dysfunction. Of 8 boys 1 was prepubertal, 3 had compensated hypogonadism and the remainder low testosterone levels with raised gonadotrophins. No second cancers occurred but 2 pts developed exostosis.

Conclusion
The addition of other treatments to the OPEC + HDM sequence increases the morbidity in advanced Nbl survivors.

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INTERACTIONS OF PREDNISOLONE AND METHOTREXATE (MTX) ON BONE IN ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

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OBJECTIVE: To distinguish between adverse effects of disease & treatments on bone in children with ALL.
METHODS: Longitudinal measurements of bone turnover markers at 2-6 weekly intervals in 20 children undergoing chemotherapy for ALL (UKALL XI protocol). Following induction & first intensification, children were randomised to two groups for subsequent CNS-directed therapy: intrathecal (it) MTX (n=8) or high-dose (hd) MTX (n=12).
RESULTS: The table shows mean SD scores relative to age-matched controls:

Chemotherapy	PICP		BALP		ICTP	
Stage	it	hd	it	hd	it	hd
At diagnosis	-1.90	-1.67	-2.13	-1.70	-1.06	-0.01
Post-1st intensification	-5.02	-3.50	-2.16	-1.90	-1.76	-1.40
During CNS-treatment	+2.67	+0.39**	-0.31	-1.49*	+0.39	+1.79*
Pre-2nd intensification	+1.54	+0.47	-0.25	-1.03	+1.40	+1.37

[PICP = procollagen type I C-terminal propeptide; BALP = bone alkaline phosphatase; ICTP = C-terminal telopeptide of type I collagen]
* P<0.05, ** P<0.01 compared to it-MTX

Following suppression during induction & 1st intensification (P <0.05), bone turnover markers increased after prednisolone was stopped (P <0.01), but it- & hd-MTX groups differed in the extent of the increase. For all children at diagnosis, IGF-I (-1.70SDs) & IGFBP-3 (-0.88SDs) were low & urinary GH high (+24.4SDs); they normalised during induction, showed no significant post-steroid increase & did not differ between it- & hd-MTX groups.
CONCLUSIONS: ALL itself caused GH resistance & low bone turnover, affecting bone formation (PICP, BALP) more than bone degradation (ICTP). During induction & first intensification, prednisolone further suppressed osteoblast proliferation (PICP), by direct action on bone not mediated through the GH axis. The post-steroid increase in bone turnover was also independent of the GH axis & modulated by hd-MTX: osteoblast recovery was depressed by hd-MTX & osteoclast activity enhanced. Although the effect of hd-MTX was apparently short-lived, it may have occurred at a crucial period for recovery of bone architecture after steroid administration, with increased risk of later osteoporosis.

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THYROID DYSFUNCTIONS IN LONG TERM SURVIVORS OF CHILDHOOD HODGKIN'S DISEASE : A PRACTICAL APPROACH TO MANAGEMENT IN DEVELOPING COUNTRY

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In order to assess the long term effects of neck irradiation, we studied 52(45M,7F) of 84 survivors(Off Therapy and Disease Free > 2 yrs) of childhood Hodgkin's Disease registered in ACT(After Completion of Therapy)Clinic between Feb'91-Dec-96. Median age at time of radiotherapy was 10 yrs(4-18.5 yrs) and dose of radiotherapy was 3500 cGy(2000-5000 cGy). 49/52 had in addition received chemotherapy. Median duration of follow up since radiotherapy was 6 yrs(2-23.5 yrs). Clinically, 51 were euthyroid, 1 was hyperthyroid and none was hypothyroid. Thyromegaly was seen in 9/52(4-diffuse, 5-nodular). Tc scan done in 6/9, showed hot nodule in 1, cold in 4 and warm in 1. FNAC done of 4 cold nodule showed benign follicular cells. T4 and TSH estimation(by RIA method) could be done in 48/52 survivors at registration in ACT clinic and at subsequent yearly follow up. Elevated T4 and decreased TSH was observed in one clinically thyrotoxic survivor. TSH was elevated in 30/47(64%) survivors with normal T4. 25/30(Gr-A) who had upto 4 fold rise of TSH(<20 mIu/ml) were kept under observation. While 5/30(Gr-B) who had>4 fold rise of TSH (> 20 mIu/ml) were offered replacement therapy after confirmation with repeat thyroid profile. 16/25 in Gr-A on follow up showed that 14 had TSH values within the same range while 2 showed progressive increase in TSH and required therapy. Gr-A followed growth curve normally. In Gr-B, TSH decreased to <20 in 1/5 and has been subsequently observed. 3/4 while receiving L-thyroxine defaulted and showed decreased T4 in addition to raised TSH and 2/3 also showed growth retardation during that period. Our results indicate that Gr-B children should be given replacement therapy with L-thyroxine as this group tends to progress to hypothyroidism(↓T4 and growth retardation) if left unrelated. While those in Gr-A may be followed up yearly, replacement therapy being reserved for those with progressive increase in TSH. Compliance with lifelong L-thyroxine therapy, though cheap, is a major problem and default in therapy may lead to wide fluctuations in T4 levels. This practical approach is perhaps safe and viable option in developing country.

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Long-term Follow-up of Pulmonary Functions in Childhood Hodgkin's Disease Treated With Radiotherapy and Chemotherapy

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The excellent results in the treatment of Hodgkin's disease have focused much attention on the long-term adverse sequellae of therapy.
Materials and Methods: Pulmonary functions were evaluated in 46 patients, ages between 6 and 27 treated for Hodgkin's disease. Twenty-four patients were treated with median 3415cGy mantle field radiotherapy and combination chemotherapy (MOPP, ABVD, ABVD/MOPP) ***(Group 1)***. Twenty-two patients were treated with involved or extended field radiotherapy and/or combination chemotherapy ***(Group 2)***. The mean duration of follow-up after completion of their therapy was 5.4 years and the median cumulative dose of bleomycin was 83.2mg. All patients were tested by chest radiographs, spirometry and 26 patients were tested by carbon monoxide diffusing capacity (D_LCO). **Results:** Twenty-five patients (%53) had one or more abnormalities on chest X-ray. Abnormal roentgenogram findings in group 1 were %71 while this ratio was %36 in group 2 ($p<0.05$). Abnormal X-ray findings in patients treated with chemotherapy regimens containing bleomycin and MOPP were %53 and %58, respectively ($p>0.05$). Pulmonary function tests were abnormal in 24 patients (%52). Abnormal pulmonary function test findings in group 1 and group 2 were %67 and %36, respectively ($p<0.05$). Pulmonary test abnormalities in patients treated with the regimens containing bleomycin and MOPP were %53 and %63, respectively ($p>0.05$). Only in 2 patients out of 26 (%8) were the D_LCO test results abnormal. **Conclusions:** Our study suggests that on long-term follow-up after treatment, therapy with these regimens results in abnormal pulmonary function tests and chest roentgenogram findings even in asymptomatic children. These abnormal pulmonary functions are related mostly to high dose mantle field radiotherapy rather than bleomycin.

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MYELODYSPLASTIC SYNDROME IN CHILDREN AFTER CHEMOTHERAPY FOR NEUROBLASTOMA

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Myelodysplastic syndrome(MDS) is one of the serious side effects of chemotherapy for neuroblastoma(NB). We studied the clinical characteristics of MDS in patients(pt) receiving chemo-

therapy for NB at our institution.
We reviewed eleven pt(one with stage Ⅲ NB, ten with stage Ⅳ NB) treated by the protocol proposed by the Japanese study group consisting of cyclophosphamide, vincristine(or VP16), pirarubicin, and cis-platinum between January 1985 and October 1994. On morphologic analysis of the peripheral blood and bone marrow aspirates three pt showed bone marrow dysplasia involving two or three lineages. According to FAB criteria the morphology was classified as refractory anemia in two and refractory anemia with excess blasts in one(pt1). On cytogenetic analysis of aspirated bone marrow, these pt showed chromosomal abnormalities, 46,XY,17q+, 18q-(pt1), 45,XY,-7(pt2) and 46,XX,inv(11)(q21;q23)(pt3),respectively. Rearrangement of MLL gene on chromosome 11q23 in pt3 was detected. The pt had residual diseases after completion of the protocol and received additional chemotherapy resulting in higher drug doses than that given to other pt without MDS. Median total drug doses administered to pt with MDS were 28,250 mg/m² for cyclophosphamide, 941 mg/m² for pirarubicin, 1,815 mg/m² for cis-platinum, and 2,433 mg/m² for VP16. Median total doses of both pirarubicin and cis-platinum administered to pt with MDS were significantly higher than those administered to pt without MDS(p =0.008,0.003). Two of three pt with MDS died of acute myeloid leukemia(pt1) and recurrence of tumor,respectively.
These results indicate that the protocol of the Japanese study group has the potential to induce myeloid neoplasm in patients receiving additional chemotherapy.

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DEVELOPMENT & EVALUATION OF AN INFORMATION BOOKLET FOR ADULT SURVIVORS OF CHILDHOOD CANCER.

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With the increase in survival following cancer in childhood and adolescence there is a need for futher information for these survivors relating to their treatment & possible late effects. The above group has developed a booklet to provide written information directed at young survivors age 14 yrs and above. The first section provides information applicable to all survivors & comprises the rationale for long term follow up, general advice about a healthy lifestyle & information about employment & life insurance problems. The second provides specific information relating to issues applicable to the individual concerned, including a treatment summary.

Fifty survivors took part in an evaluation of the booklet.The aims of the evaluation were 1) to assess the need for a booklet by determining survivors existing knowledge of their illness, treatment and possible late effects 2) to determine the acceptability of the booklet 3) to assess any increase in knowledge & influence on health related behaviour gained from reading the booklet.

The results of the evaluation showed that 72% felt they had a lack of understanding about their illness, treatment and possible late effects and 62% wished for futher information . 87% found the booklet was easy to understand. After reading the booklet 42% had an increased awareness of health related behaviour and 95%rated attendance at long term follow up as important. These results suggest that providing written information in this format is an effective supplement to discussions in long term follow up clinics. The published booklet will be on view with the poster.

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THE INCIDENCE OF ACUTE RENAL DAMAGE AFTER METHOTREXATE ADMINISTRATION IN CHILDREN

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Nephrotoxicity is a potential hazard following high-dose methotrexate (HDMTX) therapy.
In this study we analised the incidence, type and severity of the acute renal damage caused by HDMTX (>1 g/m²/d) in children with malignancies. Glomerular filtration rate (GFR), proteinuria and tubular functions before, one and two days after of 147 HDMTX courses in 43 children (18 girls, 25 boys, mean age: 12.6±4.8 years) were examined.
Mean GFR did not changed after HDMTX (before treatment: 82.3±38, one day after: 90.4±52, two days after: 81.2±36 ml/min/1.73 m²), but in 21 % of the cases significant decrease (>20 ml/min/1.73 m²) in GFR could be detected. None of the patient had acute renal failure. Significant proteinuria was found in 42.6 % of the cases after therapy (th). Mean urinary protein excretion were 0.12±0.1 before, 0.26±0.16 on day1 and 0.31±0.26 g/m²/d on day2 after treatment. Urinary calcium excretion was elevated in 40% and tubular phosphate reabsorption was decreased in 21% of the cases on day1 or day2 after HDMTX. Urinary N-acetyl-β-D-glucosaminidase was elevated in 48% before th, and showed acute increase in further 39% after HDMTX administration. Microalbuminuria (>30 mg/1.73 m²/d) was detected in 48.5% of the cases (urinary albumin excretion before th: 10.3±11.9, after th: 65.4± 78.1 mg/m²/d). We found negative correlation between the intensity of hydration regimen and proteinuria (p=0.03), between age and decrease in GFR (p=0.02) and positive correlation between age and proteinuria (p=0.038).
In conclusion, acute nephrotoxicity without acute renal failure is a frequent problem after HDMTX therapy. Changes in tubular functions may be early signs of renal damage.

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5 YEAR FOLLOW UP OF IFOSFAMIDE INDUCED NEPHROTOXICITY IN CHILDREN WITH CANCER

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This study aimed to document changes in renal function over time and to confirm risk factors for nephrotoxicity after ifosfamide treatment. 39 children and adolescents (26m; aged 0.6-18.1 years, median 6.2) treated with ifosfamide (mean dose 111 g/m², range 12-153), but not cisplatin or carboplatin for childhood cancer had renal function investigated 1 and 6 months post-treatment and then annually for 5 years. GFR, measured by ^{51}Cr EDTA clearance, serum carbon dioxide (SCO_2), the renal tubular threshold for phosphate (Tm_p/GFR), and early morning urine osmolality (EMUO) were measured. We have described a scoring system for ifosfamide nephrotoxicity (NTX score) based on these measurements.

The mean fall in GFR from 1 to 6 months after treatment was 31 (p= 0.006). Tm_p/GFR, SCO_2, EMUO, and GFR after 6 months did not change significantly over 5 years. The mean of each of these observations for each patient was calculated, and the results are summarised below:

	Mean	Range	Normal range
GFR (1 m) (ml/min/1.73m²)	105	67 to 244	> 90
Mean GFR (≥ 6 m) (ml/min/1.73m²)	85	44 to 126	> 90
Mean Tm_p/GFR (mmol/l)	0.83	0.02 to 1.42	1.0 to 1.78
Mean SCO_2 (mmol/l)	21	12 to 25	> 20
Mean EMUO (mosmol/l)	705	393 to 972	>600
Mean NTX score	3	0 to 10	0

Cumulative dose of ifosfamide was significantly associated with mean SCO_2 (p=0.006), mean Tm_p/GFR (p=0.002), and mean NTX score (p=0.003). Age at which treatment commenced was significantly associated with mean SCO_2

(p=0.001), mean EMUO (p=0.01), and mean nephrotoxicity score (p=0.014)

This study confirms observations of the early fall in GFR after treatment with ifosfamide, but Tm_p/GFR, SCO_2, EMUO, and GFR after 6 months remained reduced but stable. Renal damage did not significantly change in the 5 years after treatment with ifosfamide. Impairment in renal function is therefore likely to persist in the medium term. Cumulative dose of ifosfamide and younger age at diagnosis are confirmed as risk factors for ifosfamide nephrotoxicity.

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ANTERIOR MEDIASTINAL MASS POST-CHEMOTHERAPY FOR LYMPHOMA: RECURRENCE VS THYMIC HYPERPLASIA

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Objective: To evaluate anterior mediastinal masses (AMM) in children post chemotherapy for Non-Hodgkin's lymphoma (NHL).
Methods: Review of medical records of children treated for NHL at MCO. Only patients whose evaluation of AMM included CT Scans, gallium scans and/or biopsy of the mass are reported in this study.
Results: Of 44 children treated from 1976 - 1996, 9 (20%) children were found to have an AMM post therapy for their NHL. The M:F ratio was 2:1. The primary sites were mediastinal (4), supraclavicular (3) and abdominal (2). Age at diagnosis ranged from 3.5-16.5 years (median 7.5). All were treated on standard protocols of the CCG. Duration of therapy varied from 6-18 months. None received any radiation therapy to the mediastinum. An AMM was visualized by CT Scan from one to 18 months post therapy in 8 children. In one patient, a mass was seen 10 months into therapy. When further diagnostic tests were performed, all 9 children had negative gallium scans. In addition, three children, including the one whose mass was visualized on therapy and two with mediastinal primaries, underwent a biopsy of the mass. All three revealed normal thymic tissue. All 9 children have now been followed for a period of 1 month - 5.5 years (median 4 years), and they continue to remain in remission with decreasing size of the soft tissue mass.
Conclusions: Thymic hyperplasia and/or rebound growth can simulate a recurrence of disease in children. Gallium scans may be used to differentiate thymic hyperplasia from lymphomas.

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MITOCHONDRIAL DNA DELETION IN CHILDREN WITH DE TONI-DEBRE'-FANCONI SYNDROME SECONDARY TO ANTIBLASTIC THERAPY

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<u>OBJECTIVE.</u> Children with malignancies, who receive chemotherapy, are at risk of developing secondary De Toni-Debrè-Fanconi syndrome (DDFs). The aim of this study is to verify whether in the pathogenesis of secondary DDFs there are deletions of mitochondrial DNA (mtDNA) and disorders in oxidative phosphorilation complex (OPC), as reported in patients with primary DDFs.
<u>METHODS.</u> We studied 18 paediatric patients with solid tumours, previously treated with chemotherapy, who were off therapy for at least 1 year. All of them had normal renal function at diagnosis. Only four of them received ifosfamide (IFO) and platinum compounds. For all patients we evaluated: i) renal function; ii) activities of OPC measured on platelets; iii) mtDNA, extracted from platelets, amplified by PCR, using specific primers to detect the common deletions which were further confirmed by primer shift PCR method.
<u>RESULTS.</u> Only two patients, both treated with IFO and carboplatin, respectively for Wilms tumour and germ cell tumour, developed DDFs, 1 and 3 years after they stopped therapy. They had a decrease in activities of OPC, statistically significant only for NADH-cytochrome-c-reductase and cytochrome-c-reductase. Both children showed also a 650 bp not maternally inherited specific and unknown deletion of mtDNA.
<u>CONCLUSIONS.</u> Our data suggest that treatment with IFO and carboplatin could be responsible of mtDNA deletions, which could cause specific mitochondrial enzyme deficiencies and impairment of the transport rates for D-glucose, phosphate and aminoacids. Additional risk factors could be the young age and the reduction of renal tubular surface determined by nephrectomy.

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MRI OF THE BRAIN AND NEUROPSYCHOLOGICAL EVALUATION IN CHILDREN WITH ALL AT THE END OF TREATMENT AND 5 YEARS LATER

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The objective: To evaluate progression of abnormalities in the MRI of the brain and their correlation to neuropsychological examination in children with ALL after cessation of therapy.

The methods: 28 patients were evaluated by MRI of the brain and neuropsychological examination at the end of treatment and five years later. 13 patients were treated with chemotherapy and 15 patients received also cranial irradiation.

A summary: 7/27 patients had treatment related changes in the MRI of the brain in the end of treatment and 8/28 patients 5 years later. White matter changes (WMC) were observed in 4 patients. WMC had normalised in 2 patients, and 2 other patients had developed new WMC, one in the chemotherapy and one in the irradiated group. Three patients had calcifications or old haemorrhage, and 3 had atrophic changes. Two patients had more than one type of findings. IQ testing showed a decreasing trend during the follow-up, and visual retention (Benton) declined significantly in the chemotherapy group and Arithmetics in the irradiated group. The 2 patients with new WMC had an obvious decline in their IQ testing.

Conclusion: CNS changes may progress in MRI of the brain and neuropsychological evaluation after cessation of therapy even in patients treated with chemotherapy.

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PULMONARY FUNCTION TESTS IN CHILDREN AFTER TREATMENT FOR HODGKIN DISEASE

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Since radiotherapy and chemotherapy are successful in treatment of the majority of patients with Hodgkin disease (HD), it is becoming increasingly important to avoid late side effects. The aim of the study was to evaluate the influence of applied therapy on the respiratory system. We focused on pulmonary injuries in patients after treatment for HD. We investigated 42 patients between 8 and 22

years with treatment completed between 1 month and 10 years ago. 35 patients in this group had mediastinal tumor on initial diagnosis.
MVPP, ABVD or B-DOPA courses were applied according to current protocol. Number of courses depended on the stage of the disease. Children with mediastinal tumor were subjected to field radiotherapy with doses from 1440 to 3800 cGy.
Pulmonary function tests comprised spirography (VC, FEV_1%VC), flow-volume curve (MEF_{50}, MEF_{25}), bodypletysmography (TGV, RV, TLC, Raw), transfer factor for CO (TL_{CO}), compliance (C_L), and blood gases (PaO_2, $PaCO_2$, pH). We found that 29,3% of patients after treatment had VC below normal limits. 23,8% of the childeren from investigated group had also abnormal results of CL, 21%-TGV, 15,4%- TLC and 11,4%-TL_{CO}. However mean values of performed tests in the whole group were not significantly diffrent from normal values predicted for hight. We found strong correlation between TLC (r= -0,41p<0,05), CL (r= -0,56 p<0,05), TGV (r= -0,48 p<0,01) and the size of mediastinal tumor. Children irradiated with higher dose have had lower TGV (r= -0,40 p<0,05). Patients who recieved greater dose of bleomycin had worse TL_{CO} (r= -0,48 p<0,05).
We concluded that significant group of children after treatment for HD had changes in pulmonary function tests. Most of them had restrictive lung disease with imparment of diffusion capacity and compliance. These patients were asymptomatic but their pulmonary function shoud be carefully monitored for a longer period of time.

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QUALITY OF LIFE MEASUREMENT AND LATE FUNCTIONAL RESULTS IN PATIENTS WITH MULTIMODAL TREATMENT OF BONE TUMOURS

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Objective and Methods: With the increasing number of patients surviving disease free following diagnosis of malignant bone tumours and the availibility of different modalities of local therapy and limb salvage procedures late functional results and quality of life measurement have become essential. The functional evaluation score of Enneking for Orthopedic sequelae, and quality of life measurements (EORTC QLQ -C 30) are being determinated in a cohort of 267 patients with musculo-skeletal tumours surgically treated in a single institution (Münster) over the last ten year period and analysed according to data of first line tumour therapy and complications.
Results:.To date data of 267 pts.of a total cohort of 390 pts.are complete. The median age was 16 years (range 1-74 years). 109 pts were female.The diagnoses are: Osteosarcoma 136 pts, Ewing´s tumours 66 pts, chondrosarcomas 27 pts., MFH 9 pts and other musculoskeletal tumours 25 pts. Median time since diagnosis was 48 months range (9-319 months). Most patients had undergone surgery, 149/267 in combination with chemotherapy, 63/267 had also received locoregional radiation. The surgical procedures included rotationplasty, amputation, tumour resection, tumour resection with either endoprosthesis, allograft or autograft. The mean functional status of all pts. was 21.5 (of a maximum of 30) compared to 21.3 in patients with femur tumours and 18.3 in pts with pelvic tumours. The majority of pts has satisfactory quality of life measurements: Functioning scales: global health status (mean 74.7), physical functioning (mean 77.5), role functioning (mean 63.3), emotional functioning (mean 78.5), social functioning (mean70.5). Symptoms: pain (mean 22.8), financial difficulties (23.11). The results of quality of life measurements depends on localisation,surgical approach and time since diagnosis.
Conclusion: The given questionaire and examination profil allows differential functional assessment of different local therapy approaches. The analysis allow differentiation between surgical procedures and techniques.

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LATE EFFECTS OF CHEMOTHERAPY VERSUS BONE MARROW TRANSPLANTATION FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA.

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The majority of children diagnosed with AML who achieve remission can now be cured. HLA identical sibling bone marrow transplant (BMT) offers the best chance of cure and modern conditioning regimens do not include total body irradiation (TBI). We studied the late effects of therapy in all AML survivors treated at CHOP between January 1972 and December 1994. Of 256 treated, 58 were alive in first complete remission and had greater than 1 year of follow-up data available. Patients were divided in 2 groups based on whether they had received chemotherapy alone (Group A) or chemotherapy followed by BMT (Group B) Group A (N=36) had mean follow-up of 77 months and Group B (n=22) a mean follow-up of 70 months. Of note, 11 patients in Group A received cranial XRT and 7 Group B patients received TBI. Height, weight, renal, ophthalmologic, and cardiac function were assessed and compared between the groups. The mean weight Z score in Group A rose from -.10 at TO (diagnosis) to .90 at T2 (last follow-up) with a p value of < .001. The mean BMT weight Z scores at TO and T2 were .18, and -.05 respectively (p value = .55). Height Z scores in Group A were -.45 and -.48 at T0 and T2 versus -.26 and -.54 in Group B (P value = .18). Each group had 1 patient with a creatinine above the normal range. Two patients in each group had a diastolic blood pressure > 95th%ile for their age and sex. One patient in Group B receives antihypertensive medication. Six of the Group B patients who received TBI have cataracts and 1 has required surgery. Two of the Group A patients receive thyroid hormone supplementation (both have Down's syndrome) as do three of the Group B patients (2 of whom received TBI). Six Group B patients, all of whom had TBI, presently receive estrogen supplementation. The mean cardiac shortening fraction (SF) was 34% in Group A and 35% in Group B. However, two Group A patients have a SF < 28% and one requires digoxin. Of the fourteen patients who underwent allogeneic BMT, one who received a transplant from a phenotypically identical mother, has chronic extensive graft-versus-host disease. In summary, late effects of present day BMT regimens (e.g. non TBI containing) are not statistically or clinically significantly different from chemotherapy alone.

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RENAL FUNCTION IN SURVIVORS OF WILMS TUMOUR IN THE NORTH OF ENGLAND 1968-1995.

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Introduction: Management of children with Wilms tumour (WT) has improved greatly over the last 40 years with a current 5 year overall survival rate of ≥ 80% after treatment with surgery, with or without a combination of chemotherapy and/or radiotherapy. In view of concern about long term toxicity, treatment protocols have been modified in an effort to reduce morbidity without reducing efficacy. However no large comprehensive study of glomerular, and renal tubular function in survivors of WT has been carried out previously.
Aims: To determine the prevalence and nature of subclinical and overt **glomerular**, **proximal** and **distal renal tubular toxicity** in a population based cohort of survivors of WT.
Methods: Twenty-nine patients (19 female) with a median age of 3.2 years at diagnosis have been studied. 9 had a stage 1 tumour , 8 stage 2 , 6 stage 3 , 4 stage 4 and 1 stage 5. **Glomerular filtration rate (GFR)** was measured from ^{51}Cr-EDTA plasma clearance; **proximal tubular function** by electrolyte fractional excretions, phosphate threshold (Tmp/GFR) and renal tubular enzymes; and **distal tubular function** by determining the osmolalities of the first 2 urines on 3 consecutive days. A DDAVP tests was performed when all urine osmolalities were low (< 800 mOsm/kg). Blood pressure, and renal ultrasound to assess renal size, were also measured.
Results: The median (range) GFR was 97 (74 -119) mls/min/1.73m^2;and serum creatinine was 67.5 (48-116) µmol/l, 3 patients having values marginally above the reference range. The fractional excretion of sodium was normal in all patients. One patient had marginally elevated urine alanine aminopeptidase excretion. The median urine osmolality was 848 mOsm/kg; all but 2 patients

achieved at least 1 value over 800mOsm/kg. These 2 patients had an impaired urine osmolality response after administration of nasal DDAVP. Compensatory renal hypertrophy was seen in all patients. No patient had a raised blood pressure.
Conclusions: Treatment for WT in the North of England with previous and current national protocols has not had an appreciable nephrotoxic effect in the majority of patients.

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PULMONARY FUNCTION STUDY IN CHILDREN TREATED FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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The use of more aggressive chemotherapy in the management of children with acute lymphoblastic leukemia (ALL) contributes to the occurrence of impairment in the pulmonary functions. Therefore, we studied the pulmonary functions (PF) of 26 patients (11M:15F) 6 to 12 years old (mean 8.35+/-1.86) treated successfully with the BFM protocol for ALL. We tested the Tidal Volume :VT, Forced Vital Capacity : FVC, Forced Expiratory Volume in one second FEV_1 (L/Sec) , Peak Expiratory Flow: PEF(L/Sec) and Peak Expiratory Flow between 25-75% of FVC : PEF 25-75% (L/Sec). Tests were calculated before and after exercise and the results were compared with 35 healthy control group.

Results are expressed as % of the predicted values

	Control	Patients	Significance
VT	99.8+/- 10.3	97.3+/- 8.3	P>0.05 NS
FVC	95.2+/- 8.6	83.5+/- 9.3	P<0.001HS
FEV_1	93.6+/- 11.3	88.7+/- 7.9	P<0.05S
PEF	96.7+/-9.6	86.9+/- 6.3	P<0.001HS
FEF(25-75%)	97.2 +/- 6.6	85.6+/- 8.2	P<0.001HS

By exercise there is a percent decrease of all the PF, the FVC being - 8 +/- 3%, FEV1-15.6 +/- 6.3 % , PEF - 13.4+/- 3.6 % , and the FEF(25-75%) -21.9+/- 7.1% .

In conclusion : Impairment in PF tests was observed in children survivors of ALL. Despite the lack of overt morbidity, a long term study is needed to detect a possible development of later sequel and overt morbidity.

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LATE EFFECTS OF THERAPY FOR PATIENTS WITH PRIMARY ORBITAL RHABDOMYOSARCOMA: A REPORT FROM INTERGROUP RHABDOMYOSARCOMA STUDY (IRS)-III, 1984-1991.

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We reviewed sequelae in 36 patients (pts) treated on IRS-III for orbital rhabdomyosarcoma (RMS). Three pts had the globe removed, 2 after local recurrence and 1 due to treatment complications. Thirty-three pts (92%) continue with the globe in place. 27 of 33 pts (82%) had a unilateral cataract; 18 (67%) underwent cataract extraction. 23 of 32 pts with data (72%) had reduced visual acuity in the affected eye; 4 of them (17%) had unilateral blindness. The affected eye was dry in 47% of the pts and painful in 29%; 30% had unilateral ptosis. Chronic conjunctivitis or keratitis was noted in approximately 20% of pts, but only 10% had corneal ulceration, and 13% had increased tearing. Only 1 pt had retinal detachment. A hypoplastic orbit was reported in 66% of the patients, but only 21% had significant enophthalmos. 7 of 28 pts with data were referred for plastic/craniofacial surgical reconstruction. Three pts (9%) received growth hormone therapy. Twelve of 13 girls had a normal menstrual pattern, and 3 had established fertility. We conclude that the most common late sequelae of therapy for orbital RMS are unilateral cataract, decreased visual acuity, hypoplastic orbit, and dry eye. Serious post-treatment problems such as corneal ulceration, growth failure requiring hormone treatment, and retinopathy are unusual and may become even less frequent with lower radiation therapy doses and improved techniques. Supported in part by USPHS Grant CA-24507.

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Abstract withdrawn.

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INFLUENCE ON MALE FERTILITY OF CHEMOTHERAPY TREATMENT FOR NON HODGKIN'S LYMPHOMA (NHL).

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111 patients treated in Institut Gustave Roussy between march 1974 and september 1992 by the protocols COPAD (1974-1980), LMB 81-84-86-89 or LMT 81 and 89 were evaluated for fertility. At the time of therapy age was 2 to 17 ½ years (median 11 yrs) and pubertal status : 72 impubertal, 29 intrapubertal and 10 post pubertal. Exploration was based on basal dosage of FSH-LH completed by sperm count for 7 patients and performed at the age of 15 to 27 yrs (med 18 yrs) and 2 to 17 yrs (med 7 yrs) after the end of therapy.

Results : Puberty was normal for all patients. Exploration was normal for 58 patients (52 %), abnormal for 53 (48 %) with elevation of basal FSH dosage or azoospermia.

Results according to the protocol and total dose of cyclophosphamide (CPM) are resumed in the following table :

	COPAD	LMB81	LMB84 long arm	LMB 86 89 grC	LMB84 short arm LMB89 grB	LMB89 grA	LMT81
CPM gr/m²	12 (7-22)	10,2 (7,6-13)	8,3 (7,3-8,7)	6,8	5,8 (5,3-6,1)	3	5,4 (3-6)
Normal	14	8	4	1	13	2	16
Abnormal	23	10	4	3	3	-	10

Consecutive FSH dosages were performed in 42 pts and were similar except in 3 pts of the LMB 89 grB who normalised subsequently. Only 7 sperm counts were performed and showed good correlation with FSH level except in 2 pts who had azoospermia and normal FSH. Four patients fathered, (3 had normal FSH and 1 an elevation of FSH and oligospermia).

Conclusion : probability of infertility increases with the total dose of CPM and justifies the effort to decrease total dose of CPM in protocols with high cure rates.

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LONG TERM CARDIAC EFFECT OF DOXORUBICIN THERAPY IN WILMS' TUMOR SURVIVORS

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Ninety percent of 57 children treated for Wilms' Tumor in our institute between 1970-1996 are long term survivors. Thirty-eight patients (pts) received doxorubicin, of these, 4 also received lung irradiation. Cardiac function was evaluated at baseline by ECG, echocardiography and resting MUGA (in pts ≥5 years). Sequential studies were performed during treatment and at follow-up. Out of the 6 pts who died of the disease, one developed an early cardiac dysfunction; one patient was lost to follow-up. Median follow-up was 7.5 years (range 1-22). Cardiac abnormalities (Echo-SF<28%, MUGA-EF<50%,QTc interval>440) developed in 11/32 (34%) pts. In 7/11 MUGA was the first test to become abnormal, and was the only abnormal test in 3. QTc interval was prolonged in one pt. with congestive heart failure (CHF). Cardiac arrhythmias occurred in two pts. Median age at diagnosis for the abnormal group was 4.8 years (4.2 years for the whole group). 7/21 (33%) females and 4/11 males (35%) who received doxorubicin developed cardiac dysfunction. Early cardiac dysfunction (0.7-2.4 years from diagnosis) was found in 6 pts, late cardiac dysfunction in 5 pts (7-10 years). Cardiac dysfunction developed in 2/4 with lung irradiation. The mean cumulative dose of doxorubicin administered in the group with cardiac dysfunction was 380mg/m2 (300-450mg/m2) as opposed to 245mg/m2) for the group with normal cardiac function ($p < 0.0001$). Six pts with clinical symptoms received doxorubicin 408mg/m2. Median follow-up of the abnormal cardiac group was 12 years, and that of the normal group 5.5 years ($p < 0.0001$). At follow-up cardiac function in 3 pts improved. The 6 pts with moderate to severe CHF were controlled with digitalis, diuretics and ACE inhibitors.

Conclusion: Long term sequential cardiac monitoring in Wilms' Tumor survivors is mandatory. Limiting the total doxorubicin dose to < 300mg/m2 is suggested. Variation in schedules of delivery, or the use of cardioprotective agents may reduce the risk of this serious complication.

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LYMPHOMA AS FIRST OR SECOND PRIMARY TUMOURS AMONG CHILDHOOD CANCER SURVIVORS. A SPANISH MULTICENTRE STUDY.

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The Spanish Late Effects Study Group, collects information on children treated for a previous cancer. The collected data include treatment of the first tumour and possible predisposing factors to have cancer. Out of 11350 patients with a First Primary Tumour (FPT) a total of 124 Second Malignant Tumours (SMT) have been collected.

The prupose of this report is to present some subgroups of these patients.

Subgroup A: Patients who had a FPT which was a Non-Hodgkin lymphoma. This group includes 13 children diagnosed between 1974 and 1991,who presented a SPT with an average latency of 85 months (24-220) betwween 1986 and 1995. The SPT had been: 4 ANLL, 1 ALL, 3 Brain tumours, 2 Thyroid carcinomas, 2 osteosarcomas and 1 soft tissue sarcoma. 5 out of 13 are alive (medium follow-up: 57 months). All children were treated with chemotherapy (LSA_2L_2 or CHOP based regimens) and four also received local radiation .

Subgroup B: Patients who had a FPT which were a Hodgkin Lymphoma. This group includes 9 children diagnosed between 1976 and 1992, who presented a SPT with an average latency of 92 months (7-192) between 1987 and 1996. The SPT had been: 4 ANLL, 2 NHL, 1 MDS, 1 Thyroid carcinoma, 1 Epithelioma. 4 out of 9 are alive (medium follow-up: 36 months). Two children received only radiotherapy, one received only chemotherapy and the other 6 received combined treatment with chemotherapy (MOPP or COPP based regimens) and radiotherapy as treatment of their FPT.

Subgroup C: Patients who had a SPT which was a Non-Hodgkin Lymphoma. This group includes 9 children diagnosed between 1991 and 1996, who presented an FPT about 116 months earlier (25-261) between 1972 and 1994. The FPT were 5 ALL, 2 HL and 2 Brain tumours. 5 out of 9 are alive (medium follow-up: 27 months). All children except one received local radiotherapy, and 7 out of 9 received chemotherapy as treatment of their FPT.

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AML, ALL AND OTHER SECOND MALIGNANCIES AFTER TREATMENT FOR A SOFT TISSUE SARCOMA (STS) ACCORDING THE GERMAN CWS STUDY PROTOCOLS 81 TO 91

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Introduction: Second malignancy (SM) is a difficult form of „late toxicity" after multi-modal treatment - especially in children and adolescents. Due to the prior therapy and certain nature of these neoplasms they account for a respectable number of late deaths. Within the CWS protocols, which prescribe a quite intensive chemo- and radiotherapy concept, occurrence of SM is of major importance. We hereby summarise the 16 (+3) cases of confirmed SM after CWS 81 to 91 therapies, which have been registered through the last 15 years.

Patients: Characteristics could be obtained of the table (M.: months, F/u: Follow-up).

Study	CWS-81	CWS-86	CWS-91	total	Non-study
n_{total}	341	481	595	**1417**	?
regime(s)	VACA	VAIA	VACA/EVAIA	--	(E)VAIA
Radioth.	3/4 (75%)	4/9 (44%)	0/3 (0%)	**7/16**	
F/u (med.)	72 M. (52-185)	59 M. (34-136)	30 M. (18-71)	**50 M.**	--
n_{SM}	4 (1.2%)	9 (1,9%)	3 (0,5%)	**16** (1,1%)	3
Age	5,5 y. (1-10 y.)	4 y. (1-14 y.)	4 y. (3-6 y.)	**4 y.**	35 y. (20-60)
Sex (m:f)	2:2	6:3	2:1	**10:6**	1:2
SM	1 AML, 2 Osteosarcoma, 1 Chondrosarcoma	3 AML, 2 ALL, 1 MFH / Osteosarcoma, 1 Astrocytoma, 1 Glioblastoma, 1 EES	2 ALL, 1 Retinoblastoma	--	3 AML
med. Time	102 M. (51-154)	53 M. (27-99)	21 M. (17-53)	**52 M.**	21 M. (14-84)

Results: Through all studies only 4 AML and 4 ALL (0,6%) have been registered - 1 ALL (no AML) after an etoposide containing regimen (EVAIA). All other leukaemias occurred after treatments without etoposide, but with alkylating agents and anthracyclins (VAIA/VACA). Solid SM occurred in 8 pts. (0,6%), but only 5/8 pts. received radiotherapy to this sites. The median time for occurrence of SM obviously decrease by therapy intensification as done in protocol evolution ('81->'86->'91). 3 additional adult pts. - not treated within the protocol, but with same regimen (2 EVAIA, 1 VAIA) - developed AML very rapidly, indicating their potentially higher vulnerability to this treatment.

Conclusion: Second malignancies after CWS treatment for STS is a quite rare seen „late toxicity". Time for occurrence of a SM seem to decrease by therapy intensification. Follow-up time for CWS-91 (and probably CWS-86) is too short to give a final statement on the incidence of solid SM, but occurrence of secondary leukaemia is obviously not higher despite incorporation of etoposide. Interestingly 12/16 paediatric pts. (75%) with SM are still alive in „second" remission, indicating that even a second cure is possible.

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CUMULATIVE EFFECTS OF HIGH TOTAL DOSE OF CARBOPLATIN ON RENAL FUNCTION

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Carboplatin (CBDCA) is a platinum derivative with less nephrotoxic potential than cisplatinum. However, nephrotoxicity has been considered a dose-limiting side effect in adults. In children previous studies have demonstrated that routine monitoring of renal glomerular function is unnecessary during chemotherapy with CBDCA at 600 mg/mq, while acute renal failure is reported in a child after high dose of CBDCA infusion (2000mg/mq). There are few published data concerning the potential cumulative effects of high total dose of CBDCA (more than 5gr/mq) in children. We studied the GFR, basal and after protein load, in 13 pts affected with different solid tumours and treated with JET regimen chemotherapy (CBDCA 1000 mg/mq and etoposide (E) 300 mg/mq or CBDCA 600mg/mq and E 200mg/mq). An average cumulative dose of CBDCA was 10.6 gr/mq (range 5-19.7).The age at diagnosis ranged from 8 to 132 mo (average 58.38) The average follow-up from last chemotherapy course was 30 mo (range 3-99). Five children were nephrectomized. We studied basal GFR and GFR at 1-2-3-4 hours after protein meal (3gr/Kg). The GFR normally increased 1 hour after protein load (>30% than basal GFR).We compared the basal GFR and GFR after oral protein load in nephrectomized pts versus not nephrectomized. We did not find any statistically significative difference. We correlated the GFR with total dose of CBDCA using the r of Pearson. No statistically significative correlation was found before and after protein load.

B GFR a	1h GFR b	2h GFR c	3h GFR d	4h GFR e
118±45	228±120	239±226	213±13	153±89

a vs b $p < 0.0033$ - a vs c p NS - a vs d p NS - a vs e p NS

a: nephrectomized b: unnephrectomized

	B GFR	1h GFR	2h GFR	3h GFR	4h GFR
a	119±47	183±100	331±352	212±120	203±110
b	117±47	256±189	181±85	213±147	123±63

a vs b B GFR p NS - 1h GFR p NS - 2h GFR p NS - 3h GFR p NS - 4h GFR p NS

In conclusion the pts showed a normal basal GFR that increased to normal levels 1 hour after protein load (NV GFR 120 ± 40 ml/min/ 1.73 mq). The lack of correlation between the GFR and total dose of CBDCA indicates that there is no glomerular damage due to high total dose of CBDCA.

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Abstract withdrawn.

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INTERFERON α 2B (INTRON A) THERAPY OF CHRONIC HEPATITIS C IN PATIENTS AFTER CHILDHOOD CANCER TREATMENT

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13 patients (pts) suffering from chronic hepatitis C (7 males and 6 females, aged 7 $^{9}/_{12}$ to 25 $^{2}/_{12}$, median 16 $^{2}/_{12}$ years) diagnosed by stable elevation of transaminases, anti-HCV antibodies and/or presenting HCV-RNA were treated with interferon alpha 2B (Ifn α2B). All had previously undergone childhood cancer treatment at St.Anna Childrens hospital (8 pts acute leukemias, 3 pts non Hodgkins lymphomas, 2 pts solid tumors) and were out of chemotherapy for more than one year (median 5 $^{6}/_{12}$ yrs). Two patients suffered from co-infections (1 hepatitis B/C, 1 hepatitis B/C/D). Patients with autoimmune hepatitis or after previous interferon treatment were excluded.

The treatment plan consisted of an induction phase of one month with daily sc. injections of 3 mill. IU Ifn α2B /m^2 followed by 11 months of 5 mill. IU Ifn α2B /m^2 body surface every other day.

Hepatitis C genotyping showed type 1a once, type 1b 10 times and type 3a twice. Liver biopsies were scheduled prior to - and six months after therapy. Liver biopsy specimens at onset showed in most cases (9/13) a chronic persistent - and in only 2 pts a chronic agressive hepatitis.

In 5 pts the treatment had to be interrupted or reduced mainly due to critical hematological toxicity.

During treatment all the patients showed a reduction in the expression of HCV-RNA as detected by quantitative PCR. In 5/13 patients HCV-RNA expression was negative during interferon therapy for some time. 2 of these pts stayed negative for HCV-RNA more than six months after cessation of treatment. In 7 pts liver biopsy specimens before and after treatment could be compared: 3 showed an improvement - 2 had deteriorated and 2 seemed unchanged over therapy.

The primary goal of clearance from hepatitis C virus expression could only be achieved in two patients but there was an improvement of the general state in all patients.

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Feasibility of intraoperative high-dose rate brachytherapy (IOHDR) to boost external beam radiation therapy (EBRT) in children.

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Purpose: To determine if a single intraoperative brachytherapy dose can be used in conjunction with low dose EBRT to treat soft tissue malignancies in children with reduced morbidity.

Methods: From March 1992 to February 1995, six pediatric patients (4 boys, 2 girls; ages ranging from 4 to13 years; median 10.5 years) were treated with IOHDR in conjunction with EBRT, chemotherapy, and radical surgery at nine sites. The IOHDR dose was 10 Gy (at 7 sites with microscopic residual disease) or 12.5 Gy (at 2 sites with minimal gross residual disease) prescribed at 0.5 cm depth. The treatment volume varied from 9 to 96 cc (mean 30.3 cc). IOHDR was used in these patients because the tumor locations prevented positioning and insertion of conventional intraoperative electron beam applicators. The EBRT dose was limited to 27-30.6 Gy (median dose 27.4 Gy) postoperatively in all patients to minimize growth retardation or altered organ function.

Results: All patients are locally controlled after a median follow-up of 32 months (range 13-47 months). All the patients are alive, without evidence of disease in five. The other patient with stage IV undifferentiated synovial sarcoma developed regrowth of pulmonary metastases after complete remission with polychemotherapy and 14.4 Gy whole lung irradiation. Toxicity was seen in two patients. One patient with a vaginal rhabdomyosarcoma recurrent in the inguinal and pelvic nodes developed recurrent urinary infections and ureteral stenosis after 6 months and required a left nephrectomy. Another patient with an orbital mesenchymal chondrosarcoma developed mild to moderate loss of visual acuity and impaired orbital growth after 6 months.

Conclusion: It is feasible to use IOHDR in conjunction with low dose EBRT to treat pediatric soft tissue sarcomas with acceptable toxicity.

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TREATMENT OF ADVANCED NEUROBLASTOMA USING A NEW TECHNIQUE FOR TOTAL BODY IRRADIATION

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Advanced stage neuroblastoma has a less than 20% chance for long-term disease-free survival. When more than two unfavorable factors are present survival is even poorer. Bone marrow infusion following a conditioning regimen combining systemic chemotherapy, surgical debulking, locoregional irradiation and fractionated total body irradiation (TBI) has shown improved long-term disease-free survival.

From February, 1992 to February, 1997, 13 children underwent BMT for advanced neuroblastoma (Stage IV). Ages ranged from 18 months to 6 years with an average of 3 ½. There were 10 boys and 3 girls included in this group. Radiation therapy for BMT preparation included locoregional radiotherapy to all areas of disease at presentation. TBI was used in a fractionated technique. Eleven patients had autologos and three allogenic BMT's.

Radiation therapy (RT) for BMT preparation included involved field (IF) or extended field (EF) RT to bulky sites of disease at presentation followed by hyperfractionated TBI. For delivery of TBI we used a novel technique with the aid of a newly designed rectangular transparent lucite box in which the patient becomes part of the water phantom. This facilitates the radiation dosimetry with more uniform radiation dose delivery and minimizes patient set-up time. Remission was obtained in 5 patients for 6, 13, 22, 40 and 46 months respectively. Relapse and death occurred in the remainder of the patients at 5, 6, 12, 13 and 30 months after BMT.

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P-156

LATE SEQUELAE OF DEFINITIVE RADIOTHERAPY(RT) FOR CHILDREN AND ADOLESCENTS WITH HODGKIN'S DISEASE (HD)-- ST. JUDE EXPERIENCE.

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114 patients (pts) with supradiaphragmatic HD underwent RT as initial therapy between 1970 and 1995. We analyzed thyroid abnormalities, cardiopulmonary dysfunction, musculoskeletal(MS) changes, and subsequent benign tumors (BT) and malignancies (SM). Median age at diagnosis was 14.7 years (yrs) (range 3.7-23.6); 43% were female; 89% were white. 52% underwent lymphography (LAG); 62% underwent staging laparatomy. Ann Arbor staging was as follows: IA-48%; IB-2%; IIA-42%; IIIA-8%. RT field comprised mantle ± infradiaphragmatic RT(88%); bilateral neck only(10%); involved-field to peripheral nodal sites only(2%). Median RT dose was 36 Gray (range 35-40). As of 2/14/97, 99(87%) pts are alive, with a median follow-up of 13.3 yrs (1.9-27.7); 10 yr actuarial overall survival is 90.6%±3.1%. **Cardiac** dysfunction was noted in 10 pts: coronary artery disease (CAD)(1), congestive heart failure(1), pericardial effusion(1), arrhythmia(2), echocardiographic abnormalities(3), fatal myocardial infarction(2)--only 1 with history of CAD, sudden death--unclear etiology(1). **Pulmonary** dysfunction comprised 5 cases of asymptomatic pulmonary function test abnormalities. **Thyroid** dysfunction was noted in 38 pts: compensated hypothyroidism (hypo)(30), clinical hypo(1), hyperthyroidism(3), and benign nodule(7). Cumulative incidence of hypo in pts receiving cervical RT increased from 14.9%±3.5% at 5 yr to 33.5%±5.4% at 20 yr. Hypo was more common (p=0.02) in pts undergoing LAG (44.9%±8.3% vs. 20.8%±8.3% at 20 yr. **MS** changes were seen in 37 pts: hypoplasia(33), scoliosis(6), other(3); 78% of these pts were treated before age 14. Younger age at diagnosis was a significant prognostic factor (p<0.01) for developing MS abnormalities (Relative Risk 1.16). Eight pts had total of 10 **SM**: breast cancer(2), basal cell cancer(3), melanoma(1), acute myelogenous leukemia(1), chronic myelogenous leukemia(1), mesothelioma(1), carcinoma-in-situ of cervix(1). **BT** included in-field dermatofibroma(2) and desmoid(1). These results indicate significant late sequelae of RT as primary treatment for pediatric HD, stressing life-long follow-up and providing further impetus for refinements in therapy.

P-157

SHORT-TERM INTENSIVE EIGHT-DRUG CHEMOTHERAPY IN BURKITT'S LYMPHOMA

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The prognosis for children with B-cell lymphomas has gradually improved in the past 15 years. On the other hand many pediatric cooperative group studies on B-cell lymphomas have also demostrated that the patients (pts) with advanced disease can be cured by short-term intensive treatment using multiple drug combination. Therefore between April 1988 and December 1992 we have used an intensive chemotherapy (CT) regimen for the treatment of 17 pts with Burkitt's lymphoma (BL), majority of whom (70%) suffered from advanced disease at diagnosis. Their ages ranged from 2 to 14 years (median 6 yrs), and there were 9 boys and 8 girls. The pts were staged according to Ziegler's classification system, one patient had stage A (5.8%), four stage A-R (23,5%) and twelve stage D (70,5). Bone marrow (BM) involvement with L3 lymphoblasts was observed in 8 cases (47%). In 6 out of 8 pts BM showed > 25% replacement with tumor cells (B-ALL). Initial presentation was with CNS involvement in 2 pts (11.7%). Treatment consisted of 8-drug combination, CTX, ADM, VCR. Pred, MTX, VP_{16}, 6-TG, ARA-C. CNS prophylaxis was performed with IT MTX and moderately high dose systemic MTX. CT was given in 11 courses at one to three weeks intervals, and total duration of treatment was only 6 months. Nine pts developed "tumor lysis syndrome", 3 required dialysis. Despite peritoneal dialysis, one child (2-year-old boy, stage D with bilaterally renal involvement) died on the tenth day of treatment from metabolic complications associated with renal failure and massive tumor cell lysis. In the remaining 16 pts, overall remission rate was 81.2% (CR 68.75%, and PR 31.25%). Three pts were lost to follow up in remission. Six pts (5 stage D with BM involvement and 1 stage A-R) relapsed (37.5%). All of the relapses occurred within 6 months following the initial diagnosis, particularly in the sites of BM and CNS. Five out of 6 pts (excluding stage A-R) were lost with progressive disease. Currently 8 pts (50%) are off treatment for 30-95 months (median 65 months). In conclusion, intensive treatment with 8 drugs was more effective for advanced stage BL as compared to the previous 3-drug regimen (COM) in our earlier series. The pts with limited disease have been highly cured with short-term intensive regimens, but BM involvement (B-ALL) at diagnosis was found to be an adverse factor in stage D pts. Therefore, we started to treat those pts with more intensive regimens i.e. Total Therapy B. Such short-term intensive chemotherapy protocols seem to be advantageous for the pts from developing countries like Turkey.

P-158

IMPROVED OUTCOME OF CHILDREN WITH B-CELL MALIGNANCIES TREATED WITH A BFM-NHL-90-BASED PROTOCOL IN ARGENTINA

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Objective: To report the preliminary results of a protocol for B-non-Hodgkin's lymphoma (B-NHL)/ B-ALL based on the NHL- BFM-90 study.
Patients and Methods: Treatment was stratified in: R1 (completely resected), R2 (abdominal tumors and LDH <500 U/L and extraabdominal incompletely resected), R3 (abdominal and LDH ≥ 500 U/L, bone marrow or B-ALL) and RCNS+ (CNS involvement). All received a prephase followed by 5-day cycles of intensive polychemotherapy blocks (*Block AA*: Vincristine/ Dexamethasone/ Ifosfamide/ARA-C/VP16 and Methotrexate 2 g/m^2; *Block BB*: Ifosfamide replaced by Cyclophosphamide, ARA-C and VP16 replaced by Doxorubicin, *Block A and B* had the same elements except for the dose of Methotrexate which was 500 mg/m^2/24 hr infusion and Vincristine was omitted, *Block CC* :HD-ARA-C, VP16 and Vindesine).R1 received A and B, R2 and R3: AA and BB (4 and 6 blocks respectively), RCNS+ received 6 blocks (AA,BB, CC; AA,BB,CC).All received triple intrathecal chemotherapy. R2 and R3 with incomplete response after 2 cycles received CC followed by AA,BB and CC. G-CSF was given after each cycle.
Results: From January 1994 to December 1996, 41 patients with B-NHL/B-ALL were enrolled (39 eligible). Median follow-up is 18 months. Two-year pEFS is 0.76 (SE 0.07).Results according to risk group are: R1 (n=3)pEFS= 1, R2 (n=16) pEFS=0.84, R3 (n=17) pEFS=0.66, RCNS+ (n=3) pEFS=0.67. Eleven patients received Block CC because of poor response (pEFS=0.73) compared with 0.55 in our previous study (MPO 25:263,1995) . pEFS of patients with abdominal tumors and LDH ≥ 500U/L is 0.8. Relapse was the major event (n=5). Three patients died on induction. Toxicity was mainly hematological and gastrointestinal.
Conclusions:An improvement in pEFS was observed, specially in patients with abdominal tumors with high tumor burden and those with an incomplete response to chemotherapy.

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ALL IN INFANTS: 10-YEAR EXPERIENCE OF THE CZECH PAEDIATRIC HAEMATOLOGY GROUP

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The experience of the Czech Paediatric Haematology Cooperative Group with infant ALL is presented. Over 10 years (1986-1995) 21 infants (10 boys, 11 girls) younger than 12 months had been identified among 675 children and adolescents (0-18 years old) with ALL in the Czech Republic, i.e. 3%. They were managed either by BFM-83 for non B ALL (11 pts), or BFM-90 for non B ALL (10 pts). Their medical records were reviewed and the relevant data extracted, managed and analyzed. Early death occurred in 4 patients (19%). Resistant disease was observed in 4 patients (19%), too. The complete response rate was 62%, i.e. 13 patients, of whom 4 were late responders and 6 early relapsed. A second brief remission lasting one and four months was achieved by retrieval strategies in 2 cases. All relapsing patients ultimately died of their disease. Only 7 patients (33%) are so far alive in 1.CCR for 41-85 (median: 72) months as contrasted with the 63-71% long-term EFS for the entire population, thus underlining the overall poor prognosis of infants with ALL. The disease is however heterogeneous enough as to warrant international collaboration with the aim of identifying significant independent prognostic factors which would form a rational basis for evolving risk-tailored therapeutic strategies.

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IMPORTANCE OF L-ASPARAGINASE (ASP), DETRIMENTAL EFFECTS OF ADDITIONAL CYTOSINE-ARABINOSINE (ARA-C) AND OF IV 6-MERCAPTOPURINE (6-MP) IN THE TREATMENT OF LYMPHOBLASTIC NON HODGKIN LYMPHOMA (LB-NHL) : RESULTS OF THE EORTC 58881 RANDOMIZED TRIAL.

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From 10/89 through 6/96 the EORTC 58881 trial was open to ALL and LB-NHL patients. 118 pts with LB-NHL were registered and 105 are evaluable so far.

Patients:

Murphy stages	*I*	*II*	*III*	*IV*	*Sex*	*F*	*M*
	8	10	48	39		40	65
Age(y)	*0-2*	*2-10*	*> or = 10*				
	5	63	37				
initial CNS involvement		3					
initial mediastinal enlargement		73					
B-lineage = 10		T-lineage = 95					

Treatment: the treatment regimen was according to BFM scheme and included 3 randomized questions : (1) the value of Erwinia as compared to E.Coli Asp in terms of toxicity and efficacy (10 000 U/m2, twice a week, 8 times during induction protocol IA and 4 times during late intensification protocol IIA, (2) the value of high doses ara-C (HD-Ara-C) 2x1 g/m2 combined with high doses methotrexate (MTX) during interval therapy, (3) the value of monthly iv 6-MP (1 g/m2) during maintenance.

Results:

	complete response (CR)		partial response (PR)		
by the end of prephase	20		71		
at completion of IA	78		23		
			Murphy Stage		
at 5 years	*all pts*	*I*	*II*	*III*	*IV*
event free survival (EFS) %	77	100	88	74	72
overall survival (S) %	88	100	100	88	82

There is a trend towards a higher EFS in those pts in CR at the end of the prephase. S is significantly higher in the E.Coli compared to the Erwinia Asp arm (100% vs 74% p=0,01) in pts treated without additonal Ara-C (97% vs 71% p=0,02) and in those treated without iv 6-MP (100% vs 76% p=0,01).

Conclusion: (1) Conventional BFM protocol is highly efficient in LB-NHL. (2) As in ALL, E.Coli Asp is more efficacious than Erwinia Asp when used in the dosage schedule of the BFM protocol. (3) Asp is of major importance in the treatment of LB-NHL. (4) The addition of HD-Ara-C during interval therapy and of iv 6-MP during maintenance was detrimental, possibly through jeopardized compliance to the other treatment components. (5) In future decreased treatment intensity might be considered for good risk patients and more intensive therapy for high risk groups only.

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UPDATED RESULTS OF THE LMB - 89 AND BFM-90 PROTOCOLS FOR CHILDHOOD B-CELL AND T-CELL LYMPHOMA. REPORT OF THE POLISH PEDIATRIC LEUKEMIA LYMPHOMA STUDY GROUP (PPLLSG).

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From 1993 to 1996 96 children aged from 11 mths to 17 yrs with non-Hodgkin lymphoma (NHL) were included to the multicenter study. B-cell NHL was diagnosed in 59 children (61.5%), T-cell NHL in 37 pts (38.5%). The B-NHL was treated with the LMB-89 protocol whereas the T-NHL with the BFM-90.

B-NHL. Three (5.0%) pts presented st.I, 11(8.7%) st.II, 21(35.7%) st.III and 24 (40.6%) stage IV. There were 31(52.5%) primary tumor sites in abdomen, 10(17.0%) in tonsils, 4 in head-neck, 5 in nodes, 3 in skin, 2 in testes and 3 elsewhere. In 21(68.2%) children extensive tumor was diagnosed. Three pts (5.0%) were treated in group A, 37 (62.7%) in group B, and 19(32.3%) in C. The overall rate of CR in the whole B-NHL group was achieved in 56 pts (94.9%). In 3 children CR was not achieved (all in st.IV, advanced disease). Five (8.9%) pts relapsed 6 - 9 mths after beginning of treatment (3 pts with extensive tumor and 2 pts with late CR). Nine pts died : 4 in progression (relapse), 2 due to refractory disease (one with orbit and one with primary tumor site in ovary), 3 because of toxicity of the chemotherapy (1- sepsis, 1- tumor lysis syndrome, 1- brain hemorrhage). Probability of EFS is 81.0% for all B-NHL pts - 100.0% for the group A, 91.0% for the group B and for the group C 67.0%. Estimated EFS is 100.0% for st. I/II, 95.0% for st.III and 56.0% for st.IV. LMB-89 protocol produced high cure rate in B-NHL stage I-III. Unsatisfactory results in stage IV may be related to primary tumor site in 6 pts (orbit, CNS, stomach, ovary, neck). In 4 pts extensive tumor mass might be responsible for the failure.

T-NHL. Two (8.1%) children had st.II, 13 (35.1%) st.III and 21 (56.8%) st.IV. There were 20 (54%) primary tumor locations in mediastinum, 8 (21.6%) in peripheral lymph nodes, 2 in head-neck, 2 in bones, 1 in CNS, 1 in abdomen and 3 elsewhere. The overall rate of CR in the whole T-NHL group was achieved in 32 pts (87%).Two children (1-primary CNS involvement, 1- extensive tumor in thorax) failed to achieve CR and died, 2 pts died before CR because of sepsis and hemorrhage. Five pts (15.6%) relapsed 8 - 15 mths after beginning of treatment. There where 4 pts with extensive tumor in mediastinum. Nine pts died: 5 in disease progression (relapse), 2 because of refractory disease, 2 due to toxicity of chemotherapy (1- sepsis, 1- hemorrhage from alimentary tract). Probability of EFS is 69.0% for all T-NHL pts, 68% for st.III and 77% for st.IV. Unsatisfactory results in st.III may be related to high rate (72%) of pts with extensive tumor in mediastinum.

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Effective and Safe Management of Hodgkin`s Disease in Children, Employing Intensive Multidrug Chemotherapy and Reduced Radiotherapy.

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Materials and Methods. Sixty-three patients with previously untreated Hodgkin`s disease (HD), their age ranging from 4 to 15 years (mean 9) were administered therapy from 1990 through 1995. Five of them had stage I, 20 — stage II, 27 — stage III, 11 — stage IV. Male:female 3.4:1.

To induce remission, two alternating multidrug chemotherapy (MDC) regimens were employed. The first one included chlorbutin 6 mg/m^2 per os days 1-14, vinblastin 6 mg/m^2 i.v. days 1 and 8, procarbazin 100 mg/m^2 per os days 1-14, prednisolon 40 mg/m^2 per os days 1-14. The second regimen: bleomycin 4 mg/m^2 i.v. days 1-5, vincristine 1.5 mg/m^2 i.v. day 1, dacarbazine 150 mg/m^2 i.v. days 1-5, adriamycin 60 mg/m^2 i.v. day 1, prednisolon 40 mg/m^2 days 1-5. Stage IA and IIA patients receaved 2 MDC courses, stage IIB, III, IV — 6 courses. The interval between the courses was 2 weeks.

Radiotherapy was delivered only to the lesions detected at the initial examination. The value of the total target dose on each lesion depended on the response to MDC. In case of complete remission (CR) it was 20 Gy, partial (more than 70%) remission (PR) — 30 Gy, less than 70% remission — 40 Gy.

Results. The follow-up period was from 2.1 to 6.5 years (median 4.5). After MDC completion possitive effect was registered in 94% of the patients (CR in 46%, more than 70% PR in 48%), negative effect — in 6% (less than 70% PR in 3%, no response in 3%).

For all the patients the expected disease-free 5-year survival rate was 89.4%, overall survival — 98.5%. All stage I patients (100%) were disease-free for this period, stage II — 90%, stage III — 90.3%, stage IV — 81.9%.

Conclusion. The scheme applied is of high efficacy and quite safe in the management of HD in children.

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THE N-I HODGKIN'S DISEASE TRIAL AND STUDY SPANISH PROTOCOL. PRELIMINARY RESULTS.

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The main objective of the first prospective multicentric non-randomized clinical trial EH-NI was to reproduce the good results achieved from some groups, diminishing the late effects. Applying clinical stage, the treatment strategy is based on the DAL-HD German studies and consists of:
- Stages I and IIA (non mediastinum, non extralymphatic):
  2 OPPA + 2 COM(P) + 20-25 Gy*.

- Stages IIB, III, and IV (all mediastinum and extralymphatic): 2 OPPA + 4 COM(P) + 20 Gy*.
M = MTX 5 gr/m² with leucovorin rescue after 36 hours.
* = Regions with residual tumor received 35-40 Gy.
Results: From June 1993 a total of 100 protocol patients from 29 Spanish Centers were enrolled. Median age was 10.6 years range between 3 and 16 years. Male/female ratio was 1.7 ; 35% had B-Syntoms, 58% were mediastinum and 34% were bulky disease. Stage I: 32%; stage II: 34%; stage III: 18%; stage IV: 16%. The predominant histological subtype was nodular sclerosis 57.7%. 11 Patients were excluded, 9 of them due to Procarbacine toxicity.

From 70 evaluable patients for therapy, 60 (86%) were irradiated with the standard dose to the involved areas. Only 9 (13%) patients received 35-40 Gy. The Complete Remision was of 97% and 6 patients relapsed, one of them died from progression of his disease. As on February 1997 the event-free survival (EFS) rate at nearly 4 years is 0.86% and the survival (S) rate 97%. Median follow-up is 28 months with a range between 7 and 51 months. The EFS and S rates by stage were: I = 100 and 100%, respectively; stage II = 86 and 100%; stage III = 92 and 100%; stage IV = 46 and 85%
Conclusions: The results have met aim of the trial, except for the EFS of the stage IV, though the number of the patients is too small (8).

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TREATMENT OF NON-HODGKINS LYMPHOMA (NHL) AND B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL) IN A COMMUNITY CHILDREN'S HOSPITAL - THE COOK CHILDREN'S MEDICAL CENTER EXPERIENCE

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OBJECTIVE: To review the experience treating NHL and B-ALL in a community children's hospital.
METHODS: Retrospective record review of all patients presenting to the institution with newly diagnosed NHL or B-ALL from 1983 through 1996.
SUMMARY: During the time period studied, a total of 70 patients were treated for NHL or B-ALL. Forty-three were male and 27 female; the median age was eight years. A total of 27 patients had NHL with small, non-cleaved cell (SNCC) histology; an additional 6 had B-ALL. Patients with lymphoblastic histology accounted for 21 cases, and 16 had large cell lymphoma of some type. Breakdown by Murphy stage was as follows: Stage I=1, II=10, III=41, IV=12, B-ALL=6. Most patients were registered and treated on contemporary Pediatric Oncology Group protocols. With median follow-up of 5 years, a total of 59/70 patients (84%) survive, 56/70 (80%) in CCR. The CCR rate by stage is as follows I-0/1, 0%; II-9/10, 90%; III-35/41, 85% and IV-6/12, 50%. The best CCR rate was observed in patients with SNCC lymphoma or B-ALL, with 24/27 (89%) SNCC and all 6 B-ALL patients in CCR. Of the SNCC failures, one was from second malignancy, one death in remission, and only one from relapse of primary disease. Only one patient in the series (T-cell NHL) experienced early death, due to tumor lysis complications.
CONCLUSIONS: Excellent treatment results for NHL and B-ALL are possible in a community children's hospital provided a full service oncology program and other pediatric subspecialty support is available.

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BRIEF INTENSIVE CHEMOTHERAPY PROTOCOL FOR CHILDREN WITH HIGH-RISK SMALL NON-CLEAVED CELL LYMPHOMA (SNCCL) AND ACUTE B-CELL LEUKEMIA (B-ALL)

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Between November 1989 and November 1996, 31 children less than 18 years old, newly-diagnosed with high-risk SNCCL [stage III with LDH>500iu/L (n=10) or stage IV/B-ALL (n=21)], were treated with a CNS-directed chemotherapy regimen. **Induction Phase**: cyclophosphamide, ThioTEPA, adriamycin, etoposide, vincristine, high-dose methotrexate (HD-MTX), dexamethasone plus intrathecal (IT) MTX, cytosine arabinoside (Ara-C), and hydrocortisone (HC). **Consolidation Phase**: HD-Ara-C, L-asparaginase, etoposide, HD-MTX plus IT MTX, Ara-C, and HC. **Re-Induction (and Re-Consolidation) Phases**: essentially, repeat of Induction and Consolidation at less intensity. Only the first 3 patients (pts) received Re-Consolidation. Duration of therapy as planned was 3 months (mos). Neither irradiation nor stem cell transplant were permitted. Of the 31 pts, 29 achieved a complete remission, with 2 toxic deaths in Induction (6.5%). One stage III pt experienced a local pelvic relapse at 4 mos. Three stage IV pts experienced marrow relapses at 3, 4, and 10 mos. Four pts received only Induction therapy (Rx), discontinuing after: Rx-related panmyelopathy (1), tumor-related myelopathy (1), and severe fungal sepsis (2). Two additional pts received Induction Rx followed by 1 and 3 cycles of "CHOP" Rx, due to severe Induction toxicity. Since routine incorporation of G-CSF, incorporation of prophylactic anti-fungal Rx and reduction of duration of dexamethasone in Induction, grade IV non-hemopoietic toxicities and fungal sepsis have markedly decreased in frequency. Twenty-five of 31 (81%) pts remain free of disease without recurrence from 3 to 86 mos. (median=57 mos, mean =50 mos) from diagnosis. Survival for stage III and IV pts is 90% and 76% respectively. None of 8 pts with CNS involvement at diagnosis relapsed, and no pt experienced a CNS relapse. In this group of pts at high-risk for CNS relapse, this regimen appears to prevent this development, and is associated with a significant cure rate, without the need for cranial irradiation.

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RESULTS OF UKCCSG 9003 PROTOCOL FOR CHILDREN WITH B-ALL AND STAGE IV B-NHL

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Objective: To assess the efficacy and toxicity of a short intensive multiagent chemotherapy (9003 protocol) based on the French LMB regimen.

Methods and Patients: Between June 1990 and February 1996, 63 patients with B-ALL (n=35) and stage IV B-NHL (n=28) were treated. Fifty five were male. Age range was 11 months - 16.5 years (median 8.4 years). One patient with Wiskott-Aldrich syndrome was excluded. Chemotherapy was based on high dose cyclophosphamide, vincristine, daunorubicin, high dose MTX (COPADM) and etoposide/high dose cytarabine (CYVE) with frequent I.T. medication. Cranial irradiation was used in patients with CNS disease.

Results: Eleven patients (18%) relapsed (CNS = 5, BM = 2, Combined = 3, Jaw = 1) 4 -11 months from diagnosis and one never achieved CR. All have died. In 7 of these, the treatment had to be modified or delayed because of poor clinical condition. Seven patients (11%) died of toxicity 11 days - 4 months from diagnosis. Causes of death were sepsis (n=5) or sepsis with renal failure (n=2). With a median follow-up of 2.9 years from diagnosis (range 11 months - 6.5 years), 43 patients survive (68%) in complete remission (CR).

Conclusions: Despite the very encouraging relapse free survival, the rate of toxic death was higher than in the LMB series. The use of urate oxidase in the current study may help to reduce the risk of renal complications which was a major contributory factor.

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LOCALISED B CELL NON-HODGKIN'S LYMPHOMA: IS CYCLOPHOSPHAMIDE NECESSARY FOR CURE ?

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Objective: In view of the excellent prognosis for children with localised B cell NHL the UKCCSG has progressively reduced intensity of treatment. A new study for localised disease commenced in 1990: NHL 9001. This sought to reduce long term morbidity, using a regimen without cyclophosphamide.

Methods and patients: Between June 1990 and April 1996, 74 children were registered on study. Seven are excluded from analysis (2 Hodgkin's disease, 4 Ki 1+ve histology, 1 received cyclophosphamide,). Twenty six were stage I, 40 stage II, (1 data missing). Thirty six had a primary in the head and neck, 26 localised abdominal disease, 5 in other sites.

Central pathology review is available in 55 cases (82%). Burkitt/Burkitt like accounted for 41 cases. There were 5 with lymphoblastic histology.

Results: Disease free survival (DFS) is 83% (median followup 35 months). There have been 11 events, 8 died of disease, there have been no toxic deaths. Three achieved CR with further treatment. Whilst the failure rate appears higher than on the previous trial (NHL 8501: 5 year DFS 89% 74 patients, 8 events, 2 toxic deaths), this difference is not significant (log rank test p-0.32, 2 sided test).

Conclusion: A majority of children with localised B cell lymphoma may be curable without cyclophosphamide. The challenge remains to intensify treatment for those who need it, at the same time reducing it for those who can be cured with less long term morbidity.

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CHILDHOOD B CELL LYMPHOMA - A SINGLE CENTER EXPERIENCE WITH A MODIFIED LMB PROTOCOL

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During the last 20 years, 120 children with B cell lymphoma were treated at the Pediatric Hematology/Oncology Center. Until 1986, 63 patients received an institutional protocol, and thereafter 57 patients received a modified LMB protocol (J. Clin. Oncol. 9:123-132, 1991). The modification consisted of the introduction of high dose ARA-C and etoposide to group B patients instead of CYM, and the addition of a third course of high dose ARA-C and etoposide to group C patients.
Patients' characteristics: 57 children received the modified LMB protocol. Their age ranged from 2-17 years with a median of 7 years, male/female ratio was 2:1. Eight-six percent were Jews and 14% were Arabs. Stage I disease was diagnosed in 3 patients, stage II in 14, stage III in 23, and stage IV in 17 children. The abdomen was the primary site in 34 children (61%), and the jaw was involved in 10 (17%). CNS involvement at presentation was detected in 3 patients. EBV genome was detected in 5/20 patients analyzed.
Results: 54 out of 57 children are alive disease-free with an overall event-free survival of **95%** (median follow-up of 63 months). Event-free survival for stages I, II, III patients is **100%**, and for stage IV patients **82%**. By contrast with the previous protocol in 63 children, overall event-free survival was 56% and for stage IV patients only 20%. Severe marrow suppression and neutropenic enterocolitis were the major complications of this intensive protocol.
We conclude that intensive chemotherapy with a modified LMB protocol results in a high cure rate of childhood B cell lymphoma even in patients with advanced disease.

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INTERIM RESULTS OF THE FIRST ITALIAN PROTOCOL FOR THE TREATMENT OF PEDIATRIC NON-HODGKIN'S LYMPHOMAS

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The first Italian pediatric NHL clinical trial was initiated in 1992 with the aim of treating children affected by NHL with the same therapeutic regimen in all Institutions of the Country. Secondly, we aimed at improving the average results of the treatment and the quality of supportive therapy. Therapeutic regimens used were the BFM90 protocol for B NHL, an LMT89 based regimen for non-B NHL and a modified version of the LSA2-L2 protocol for ALCL, respectively. Out of 219 patients registered, 190 were eligible: 62 females and 128 males. 111 were B cell NHL, 48 non-B NHL and 31 ALCL. Median age was 7.4, 8 and 11 years for B NHL, non-B NHL and ALCL, respectively.
163 patients reached a CR, 12 were resistant to the induction treatment, 7 died of infection before reaching a CR and 6 are at a very early stage of therapy. 168 children are alive and 138 are free of disease. EFS for B NHL is 81.5%, whereas for non-B NHL and ALCL is 64.3% and 65.1%, with a median follow-up of 16, 25 and 19 months, respectively.
The overall results of the study are lower than those of other large pediatric NHL trials, but a significant improvement compared to the various protocols previously used in our Country was observed.
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NASAL-PARANASAL ORO-NASOPHARYNGEAL LYMPHOMAS IN CHILDREN

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Objective: Most of the tumors located in the nasal-paranasal, oro-nasopharyngeal (NPONP) region are staged as early stages according to Murphy system. When TNM system used for staging, most of them are in the advanced stages. Treatment results in patients (pts) with NPONP tumors were analysed to see the effects of staging in these high risk lymphomas.
Patients and methods: Fifty-five children (median age 8 years, M/F: 4.5) with non-Hodgkin's lymphoma located in NPONP region were included in this study. Murphy staging system were used at diagnosis and the disease were re-staged by TNM system for this study retrospectively. Treatment results were analysed retrospectively.
Results: Primary localization were in Waldeyer ring, sinonasal region and nasopharynx in 45.5%, 27.3%, and 27.3% of pts respectively. 39 pts

had stage 1 or 2 disease according to Murphy system although 52 of all were re-staged as having TNM stage 3 or 4 disease. 5-yrs overall (OS) and event free (EFS) survival rates for whole group were 53.3% and 50.4% respectively. 5-yrs EFS rates were 66.6%, 59.6%, 45.4%, 0 in pts with Murphy stage 1, 2, 3, 4 disease and 100%, 64.2%, 43.8% in pts with TNM stage1,3,4 disease respectively. Treatment were intensifed in 16 of pts with early stage disease in LSA2-L2 treatment group while 4 pts with stage 2 disease treated by standard LSA2-L2 regimen. 3-yrs EFS rates in intensified and standard treatment group were 68.7% and 25% respectively.

Conclusion: More intensive regimens should be used in Murphy stage1,2 disease located in NPONP region. To predict the prognosis and treatment decisions, TNM system should be used instead of Murphy system in the tumors of these locations.

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LARGE CELL LYMPHOMA (LCL) IN CHILDREN ACCORDING TO REAL CLASSIFICATION. RESULTS OF TREATMENT WITH TWO BFM-BASED STUDIES.

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Purpose: To describe the outcome of children with large cell lymphoma at Hospital de Pediatria Garrahan in two successive BFM-based protocols.
Patients and Methods: Patients were re-classified according to the REAL classification. Pts with diffuse large-cell lymphoma *(DLCL)*, primary mediastinal large B-cell lymphoma and anaplastic large-cell lymphoma *(ALCL)* were treated with a B-cell strategy consisting of brief intensive blocks of chemotherapy according to stage (based on the NHL-BFM 86 and 90 studies with minor modifications). Peripheral T-Cell lymphoma *(PTCL)* and angiocentric lymphoma were treated with a leukemia-based protocol with an 8-drug 8-week induction phase, an M phase and delayed intensification followed by maintenance therapy until two years of treatment.
Results: From August'88 to December'96, a total of 170 NHL were diagnosed at our institution. 42 patients (24,7%) were classified as LCL . 39 /42 resulted evaluable. Median follow-up for the whole population(n=39) is 48 months. pEFS is 0,70 .There were no differences in pEFS with the remaining patients with NHL. Results according to subtype included: *DLCL* (n=18) : pEFS 0.66. Stage I-II=5,III=10, IV=3. Events: Relapse: 4; *ALCL* (n=10): pEFS 0,90. Stage I-II=1, stage III=6,stage IV=3. Six pts had extranodal primaries (bone:1, skin: 2, mediastinal:3). Only one patient had event (progressive disease). *Mediastinal large B-cell lymphoma* (n=5): pEFS 0,60. All were stage III. Two pts relapsed (one locally and the remaining one in the lung). *PTCL* (n=4): pEFS=0,5. All were stage III. All pts had extranodal primaries. Relapse: 2 . *Angiocentric lymphoma* (n=2): Both had lethal midline granuloma. Both died on induction of overwhelming sepsis.
Conclusion: A B-cell strategy is effective for patiens with *DLC, ALCL* and *mediastinal large B cell lymphoma*. However, those with *PTCL* may have a lower probability of EFS. It is not possible to determinate the efficacy of this regimen for *angiocentric lymphoma* because of the small number of patients and the high frequency of non relapse mortality

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HODGKIN'S DISEASE: A RANDOMIZED TRIAL OF CVPP FOR 3 VS. 6 CYCLES IN FAVOURABLE PROGNOSIS (FP) AND CVPP VS AOPE PLUS RADIOTHERAPY (RT) IN INTERMEDIATE PROGNOSIS.

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According to 4 criteria: Stage, Symptoms, Number of involved Areas and Age a prognostic score was designed by GATLA in 1986 (proc ASCO 7:240; 1988) and three prognostic groups were determined: Favorable (FP), Intermediate (IP) and Unfavorable.
***Patients and Methods*: A total of 194 patients (PTS) median age 8 yrs (2-16), 62 FP and 132 IP pts, were followed from Nov. '86 up to Oct '95. FP pts were randomized to receive CVPP for 3 vs 6 cycles without RT and those with IP to 6 cycles of CVPP vs AOPE. After the 3rd cycle all pts received RT 30 GY to the involved areas at diagnosis. FP pts with Bulky disease (Lymph node > 5 cm or mediastinal mass>1/3 maximal thoracic diameter) were in the IP group. AOPE:Adriamycine 45 mg/m2 iv d1, Vincristine 1.5 mg/m2 d1,Prednisone 100 mg/m2 po d1-5 and Etoposide 150 mg/m2 d1&3. CVPP: Cyclophosphamide 600 mg/m2 d1&8, Vinblastine 6 mg/m2 iv d1&8, Procarbazine 100 mg/m2 po d1-14 and Prednisone 40 mg/m2 po d1-14 ; every 28d.**
Results:

Prognosis	Treatment	# pts	%CR	%EFS at 5 years	%SV
FP	3CVPP	36	97	75	96
	6CVPP6*	26	88	80	96
IP	6CVPP+RT	92	96	83	95
	6AOPE+RT*	40	90	62	89

***This arms were discontinued by the GATLA comittee in Dec. '92 because of similar results in FP and statistically poorer results in AOPE arm.**
Three FP pts died (1 PD, 2 inCR) and 8 pts (5 PD, 3 SEPSIS) in the IP group.
***Conclusions :* Three cycles of CVPP without RT had similar EFS and SV as CVPPx6 in the FP group. CVPP +RT was better than AOPE+RT in EFS (p=0.021) but with similar SV in the IP group.**

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HODKIN'S DISEASE IN CHILDREN: DEMOGRAPHIC DATA AND TREATMENT RESULTS

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The epidemiologic pattern of Hodgkin's Disease in developing countries is different when compared with developed countries. In this study, the demographic data, results of biological studies and results of therapy of childhood Hodgkin's disease in a single institution in Istanbul, Turkey are presented. Between September 1989 and December 1996, 38 patients under the age of 16 years with biopsy-proven Hodgkin's Disease were referred to the Pediatric Oncology Division of the Oncology Institute, University of Istanbul. Twenty-eight of these patients, who were treated and followed-up only at this center are the subjects of this study.

The male female ratio was 3:1. The median age was 8.5 (3-15) years; 71 % were younger than 10 years of age. According to the Rye system, eighteen cases (64%) were classified as mixed cellularity, 4 (14%) as lymphocyte depleted, 3 (11%) as nodular sclerosis and 3 (11%) as lymphocyte predominance. One patient (4%) was classified as stage I, 8 (29%) as stage II, 13 (46%) as stage III, 6(21%) as stage IV. Eleven (39%) patients had B symptoms. Staging procedures included exploratory laparotomy in only 9 patients.

EBV VCA IgG levels were found to be significantly higher in children with Hodgkin's disease in comparison with controls. CD_4, CD_8, PHA and IgM levels were significantly lower in patients in comparison with controls. All peripheral blood DNA samples were found to be normal for p53 gene.

Treatment consisted of two cycles of ABVD chemotherapy for stages I and IIA, four cycles of ABVD for stage IIB and IIIA, six cycles of MOPP/ABV for stages IIIB and IV. All children recieved involved field radiotherapy of 15 Gy if ≤5 years, 20 Gy for 6-10 years, 25 Gy if ≥11 years old. Two patients are still on treatment. 26 had a complete response, one patient was lost to follow-up and 1 died due to sepsis. The 5 year overall survival and event free survival was 96%.

In conclusion, there is a predominance of mixed cellularity subtype, male sex and young age in our population. Results obtained with a combined modality therapy used in this institution, consisting of chemotherapy modified according to stage and low dose involved field radiotherapy are satisfactory.

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VAMP/VEPA and Low Dose Radiotherapy in Childhood Hodgkin's Disease: The Experience of the Czech Group of Pediatric Oncology.

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Objectives: Treatment of Hodgkin's disease in children should be directed at maximizing cures and minimizing the long term effects. Alkylating agents and bleomycin are two categories of chemotherapeutic agents for which alternative drugs such as methotrexate and etoposide may be reasonable choices.
Methods: We used methotrexate and etoposide in the VAMP/VEPA regimens to treat 60 clinically-staged pediatric patients with Hodgkin's disease. Twenty-nine patients with Stages I-IIA received four courses of VAMP plus low dose radiotherapy. Thirty-one IIA bulky disease, IIB-IVB patients received four or six courses of VEPA plus low dose radiotherapy.
Results: There were 6 partial remissions after the completion of chemotherapy and all of these patients relapsed, but 4 were successfully salvaged with BMT. Two patients have died. The 3.1 years overall survival is 97% (100% VAMP, 94% VEPA) and the event-free survival is 88% (97% VAMP, 77% VEPA). The only statistically significant bad prognostic factors were B symptomatology ($p = 0.01$) and treatment protocol ($p=0.04$)
Conclusions: These results suggest that VAMP is reasonable treatment for low stages of Hodgkin's disease, but more advanced disease is not adequately treated by VEPA and low dose radiotherapy. For those patients who demonstrate early relapse to VEPA salvage therapy with chemotherapy alone or autologous bone marrow transplant can be effective.

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TREATMENT OF CHILDREN WITH NON-HODGKIN'S LYMPHOMA IN TAIWAN - A REPORT FROM THE TAIWAN PEDIATRIC ONCOLOGY GROUP (TPOG) STUDY

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A nation-wide clinical trial for childhood non-Hodgkin's lymphoma (NHL) began in 1992 by the TPOG in Taiwan.
Patients and Methods: Four protocols were activated: TPOG 92LD (treatment duration:8 mo) was used for localized (stage I,II) NHL with any histology, and 92LB (2 yr), 92SNC (5 mo), 92LC (1 yr) for advanced lymphoma with lymphoblastic (LB), small non-cleaved cell (SNC) and large cell (LC) histology. From Jan 1992 through Dec 1995, 120 children with NHL from 13 member hospitals of TPOG were enrolled in this study. There were 86 boys and 34 girls. Their ages at diagnosis ranged from 2 mo to 17.3 yr with a median of 7.9 yr. Histologically, 33 were LB (27.5%), 52 were SNC (43.3%), and 35 were LC (29.2%). There were 4 (3.3%) stage I (4 LC), 13 (10.8%) stage II (2 LB, 6 SNC, 5 LC), 54 (45%) stage III (18 LB, 18 SNC, 18 LC), and 49 (40.8%) stage IV (13 LB, 28 SNC, 8 LC) diseases. Eight of the 28 stage IV SNC cases were B-cell acute lymphoblastic leukemia (ALL).
Results: Protocol violation rate was 10%.Treatment results as of Dec 31, 1996 were as follows: 4 patients were withdrawn before completing induction therapy, 5 (all SNC) toxic deaths during induction, 16 (4 LB, 6 SNC, 6 LC) failed induction, 95 achieved remission (81.9%). Eight patients dropped out during remission, 2 died during remission (1 LC with pneumonitis, 1 SNC with pneumococcal sepsis), 18 (21.2%) relapsed, and 67 (62%) remained in continuous remission with duration ranging from 10 to 57 mo. Of these 67 cases, 59 were off therapy (11 LB, 26 SNC, 22 LC) with a median remission duration of 32 mo, and 8 LB were still on therapy (median remission:15 mo). The18 relapsed cases were :2 LB_{II} (remission duration:7 & 12mo), 3 LB_{III} (6-8 mo), 1 LB_{IV} (5 mo),1 SNC_{II} (3 mo), 3 SNC_{III} (4-6 mo), 5 SNC_{IV} (1-3 mo in 4, 16 mo in1), 1 LC_{I} (2 mo), 1 LC_{III} (5 mo), and 1 LC_{IV} (23 mo). More efforts are needed to improve our treatment results.
(supported by the Childhood Cancer Foundation of R.O.C.)

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SIGNIFICANT CORRELATIONS BETWEEN DRUG RESISTANCE AND CLINICAL / LABORATORY MEASURES FOUND IN A GROUP OF CHILDHOOD *ALL* IN THE FIRST 15 DAYS OF TREATMENT

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Objective: To assess the predictive value of an MTT in vitro assay in the evaluation of leukemic cell resistance/sensitivity to cytotoxic drugs. The goal of the study was to compare results of *in vitro* drug sensitivity assay with clinical and laboratory parameters in cases of childhood acute lymphoblastic leukemia (ALL).

Study design: The chemoresistance of leukaemic cells was ascertained by means of an MTT assay in 32 children in the initial stages of ALL. The children were treated using the protocol ALL-BFM 90. Statistical correlations were made between *in vitro* drug resistance for the cytostatics, prednisolone, dexamethasone, vincristine, daunorubicine and vepesid and, the *in vivo* clinical and hematological parameters, age, sex, risk factor, leukocytes at diagnosis, absolute number of blast cells (ANBC) at day one, ANBC at day 8, ratio of ANBC at day 8 to day one, number of blast cell in bone marrow at day 15 and at day 33,and immunotyping markers CD10, CD19, CD20, HLADR, CD3, CD5, CD4,CD8.

Results and conclusion: There is a strong correlation between patient chemosensitivity and prednisolone, duanorubicine and vincristine, supporting an explanation for a common gene directing multidrug resistance. The results confirm the further use of this protocol, with the exception of 25% of patients with *in vitro* resistance to prednisolone but very good response to dexamethasone. Such patients should be treated with dexamethasone from the outset and this is likely that the genetic mechanisms in these cases follow another pathway, suggested by the lack of statistically significant correlation between prednisolone and dexamethasone, in addition.

	PREDNISOLONE		DEXAMETHASONE	
DAUNORUBICINE	r = + 0,45	**p < 0,009**	r = + 0,3072	p < 0,09
VINCRISTINE	r = + 0,51	**p < 0,003**	r = + 0,1278	p < 0,49
DEXAMETHASONE	r = + 0,34	p < 0,06		

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EVALUATION OF WHO GRADE III AND IV TOXICITY IN THE DCLSG-NHL-94 PROTOCOL

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Introduction: From april 1994 to december 1996 55 children with non-Hodgkin-Lymphomas (NHL) were recruited in the DCLSG-NHL-94 protocol: patients with B-NHL (N=36) and the LCAL patients (N=5) were treated according to the LMB-89 schedule; patients with non-B-NHL (N=14) received a treatment based on the ALL/NHL-BFM 86 strategy. The side effects were evaluated according to the World Health Organization (WHO) grading.
Results: 55 children underwent a total of 261 courses of chemotherapy:

Chemotherapy	Number of courses	Courses (%) grade III/IV toxicity
B-NHL/LCAL		
COP	30	5 (17%)
COPAD 1/2	27	15 (56%)
COPAD M1	41	21 (51%)
COPAD M2	27	15 (56%)
CYM 1/2	45	20 (44%)
CYVE 1/2	4	2 (50%)
Mainten.1/2/3/4	25	7 (28%)
Non-B-NHL		
Prot I	13	7 (54%)
Prot M	11	4 (36%)
Prot II	10	5 (50%)
Mainten.(6MP/MTX)	28	11 (39%)

Serious toxicity (WHO grade III/IV) was monitored on hematological parameters in 161/261 courses. Granulocytes < $1.0x10^9$/l were registered

in 10/27 COPAD 1/2, in 10/41 COPAD M1, in 4/13 prot I and in 4/10 prot II courses. This did generally not lead to simultaneous periods of fever and infections, but one child died of a pseudomonas sepsis after COPAD M1. Alopecia was registered in 43/261 courses, gastro-intestinal problems in 33/261 courses. This toxicity was most serious after COPAD M1 with 10/41 and COPAD M2 with 5/27 courses with serious stomatitis, vomiting and/or diarrhea. Conclusion: As expected significant hematological and gastro-intestinal toxicity was observed, but clinical toxicity was limited.

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A SURVEY OF 84 PEDIATRIC HODGKIN'S DISEASE BETWEEN 1980-1996. İSTANBUL EXPERIENCE

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84 cases (68 male, 16 female) of Pediatric Hodgkin's Disease with a median age of 7 (2-18 years) years were treated by İstanbul Medical School Oncology Group between 1980-1996. The most common physical finding was servical lymphadenopathy 89% ; hepatomegaly 56%, splenomegaly 52%, generalised lymphadenopathy (>1 region) 33%, mediastinal mass 12% were also common physical findings. Two rare presentations were abdominal mass and vena cava superior syndrome. Initial ESR was > 20 mm/h in 80% and LDH, seruloplasmine, Cu, fibrinogen was also high in 66%, 38%, 38%, 24% respectively. In only three cases, bone marrow was infiltrated. The hystopathologic classification was very typical of developing countries with Lymphocyte predominance (LP) 7,1%, Nodular Sclerosis (NS) 14,3%, Mixed Celularity (MC) 69% and Lymphocyte Depletion (LD) 9,5%. Ann Arbor staging classification was used and as a result 19% was Stage I, 29,7% Stage II , 39,3% Stage III and 12% stage IV. Exploratory laparotomy was applied to 42% of the patients and 41% had a change in their stagings (35% to higher, 6% to lower stages) For treatment MOPP± RT was used in 48,8% for a median of 75 (1-160) months with 89,2 % Overall Survival and 68% RFS ; OPPA + COPP ± RT in 26,2% for a median of 20 (5-39) months with 100% Overall Survival and 82% RFS; MOPP+ABVD ± RT in 7,1 % for a median of 44 (3-120) months with 85,7 % Overall Survival and 24% RFS ; COPP ± RT in 16.6% for a median of 68 (5-180) months with 92,3 % Overall Survival and 70% RFS in changing number of cycles according to stages. Only one case who was stage I A had only RT and relapsed after ten years in October 1995. Overall 10 year survival was 92,86% (Kaplan-Maier); and 100% in stages I and II, 93,4% in stage III and 56 % in stage IV ($P<0,05$). Histopathologic classification was not significant for prognosis ($p > 0.05$). As a result Hodgkin's Disease in childhood is a higly curable entity with a very low mortality and morbidity but morbidity is still a problem to be solved.

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LONG TERM THERAPEUTIC RESULTS IN ANAPLASTIC LARGE-CELL (ALC) LYMPHOMA IN CHILDHOOD.

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From January 1983 to December 1996, 163 consecutive pts with NHL were admitted to the III Department of Pediatrics of Bologna University. Twenty-one (12.9%) suffered from ALC lymphoma. 12 pts were males, 9 were females; median age was 11 years (range: 3-14 years). Based on the St. Jude staging system, 2 pts had stage I (9.5%), 5 pts stage II (24%), 13 pts stage III (62%) and 1 stage IV (4.5%). The most common primary sites at presentation were peripheral nodes (7 pts) and mediastinum (7 pts), followed by the subcutis (4 pts), bone (1 pt), stomach (1 pt), and lung (1 pt). Localizations in addition to the primary site were often detected: characteristic combinations were mediastinum +lymph nodes and bone+ subcutis. Systemic symptoms (bone pain, fever, weight loss) were present in 1/3 of pts.
Histological diagnosis of ALC lymphoma was performed in all cases. 13 (62%) pts had ALC, common type, 5 (23.8%) pts had ALC, Hodgkin related type, 2 (9.5%) pts had ALC, macrophage rich type, and 1 (4.8%) pt had ALC lymphohistiocytic type.
From 1983 to 1990 all pts received CT according to a modified version of the LSA2-L2 protocol. Since 1991 the chemotherapeutic regimen was modified: a consolidation phase with intermediate-dose MTX in place of ^{60}CO CNS prophylaxis and a maintenance phase with rotation of couples of drugs were included. Local RT (20 Gy) was delivered on bulky lesions in 16/21 pts. Total duration of treatment was 2 years for all stages.
Results All but 1 pt (pre-treated) were evaluable for analysis. All 20 pts achieved CR or GPR (≥ 70%) after the induction phase. Overall survival and EFS at 8 yrs are 88.8% and 71.6% respectively. 15/20 pts are alive in I CR, off-therapy after a median observation time of 69 mos (9-120 mos). 5 relapses were registered, 1 in therapy and 4 after discontinuation of treatment after a median observation time of 26 mos. In 3/5 cases relapses occurred in the primary site, in 2/3 cases in an irradiated area. 2 pts (1 relapsed on therapy) underwent BMT and eventually died without evidence of disease because of sepsis. The remainig 3 pts received chemotherapy associated with RT in 2 cases and at present 2 pts are off-therapy without evidence of disease after 112 and 22 mos from relapse; 1 pt (stage IV) is on therapy because a 2° relapse occurred 27 mos after the first one. **In conclusion**, ALC lymphoma represents a peculiar entity from the histological, biological and clinical points of view and the best chemo(radio)therapeutic protocol has not yet been established. The registration of early relapses (within 6 mos from the start of therapy) and the good results achieved with short and intensive chemotherapeutic regimens reported in the literature would indicate that this could be the best option of treatment. However, in our experience the registration of late relapses suggests that the therapy of choice is yet to be identified and that we are probably facing a variety of clinical-pathological entities with various prognoses.

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CHILDHOOD HODGKIN'S DISEASE: RESULTS OF THE ITALIAN MULTICENTRIC STUDY AIEOP-MH'89-CNR.

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The AIEOP-MH '89-CNR protocol represents the second italian multicentric study for childhood HD opened to pts registration in February1989. As of February 1996, 273 pts were registered by 29 participating Institutions. The characteristics of the 257 evaluable pts were as follows: 166 males and 91 females (M/F = 1.8), mean age 11 yrs (range 1-15 yrs). Histologic patterns were: NS 171 cases; LP 25; MC 53; LD 4; Not classified 4. As regards stage distribution, 46 pts were IA, 4 IB, 73 IIA, 31 IIB, 53 IIIA, 19 IIIB, 13 IVA, and 18 IVB. Patient population was divided into 3 chemotherapeutic groups according to clinical stage and mediastinal mass (M/T>or<0.33): group 1, (100 pts in stage I and IIA ± M/T<0.33) was treated with 3 courses of ABVD plus IF-RT (20 Gy). Group 2, (107 pts in stage IEA, IB, IEB, I-IIA with M/T>0.33, IIEA, IIB, IISA , IIEB, IIIA, IIIEA) received 2 monthly cycles of MOPP alternating with ABVD, followed by IF-RT and then 4 further cycles of chemotherapy MOPP-ABVD-MOPP-ABVD plus RT (only in pts with stage III). Group 3, (50 pts in stage IIIB and IV) was treated according to the SIOP protocol:OPPA-OPPA-COP-COPP-COP-COPP + low dose RT (20 Gy good responders; 36 Gy poor responders). Pts in stage IV were registered in the international study SIOP-HD-87.
The overall survival and Freedom From Progression rates at 7 yrs are: 94.0% and 85.1% respectively; FFP at 7 years of group 1, 2 and 3 are 91.2%, 79.0% and 82.7 % respectively. FFP by stage are 97.3%, 84.5%, 73.7%, 82.0% for stage I,II,III,IV respectively. On the basis of univariate analysis of FFP, the significant prognostic factors ($p<0.05$) were: A or B symptoms, large mediastinal mass (MM) defined as M/T ≥ 0.33 and sex. A or B symptoms maintain a statistical significance in multivariate analysis. Conclusions: the survival and EFS at 7 yrs are comparable to those registered by other cooperative groups. Group 1: the reduction of RT in terms of dosage and volume in respect to previous study, combined with 3 cycles of ABVD, produced a very satisfactory FFP rate. Group 2: the anticipation of RT after 2 cycles of MOPP/ABVD instead of after 6 cycles as in the previous study did not provide any significant benefit on the outcome: a good result was achieved but not satisfactory yet. Group 3: the FFP rate is very good. It is relevant that the FFP rate registered in stage IV pts is one of the best result reported in the literature.
The real success of this therapeutic approach will be based not only on the long-term results but also on the entity of the late side effects.

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RESULTS OF TREATMENT OF STAGE IV HODGKIN'S DISEASE

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